

April 5, 2019

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Citizen Petition Requesting the Food and Drug Administration (“FDA”) to
Revoke Orphan Drug Designation for Sublocade (Buprenorphine Extended-
Release) Injection for Treatment of Opiate Addiction in Opiate Users

Dear Sir or Madam:

On behalf of Braeburn, Inc. (“Braeburn”), the undersigned hereby submits this Citizen Petition pursuant to 21 C.F.R. §§ 10.30 and 316.29 and section 526 of the Federal Food, Drug, and Cosmetic Act (“FFDCA”), 21 U.S.C. § 360bb, to request the Commissioner of Food and Drugs to revoke orphan drug designation (“ODD”) for Sublocade (buprenorphine extended-release) injection for treatment of opiate addiction in opiate users (currently referred to as opioid use disorder (“OUD”)). Such action is necessary to (1) preserve the integrity of the Orphan Drug Act against inappropriate, unintended and abusive “evergreening” tactics, and (2) prevent such tactics from stifling the development and marketing of innovative new buprenorphine treatments to combat the growing opioid epidemic. The foundation of this request is based on the following critical factors:

- Sublocade is not now, nor was it ever, a *bona fide* orphan drug, particularly since more than two million Americans currently are afflicted by opioid addiction.
- Sublocade, which is expected to be a “blockbuster” drug with peak sales of more than \$1 billion per year, nevertheless received ODD from FDA. FDA’s decision appears to be based on an informal policy allowing the Agency to rely solely upon a *prior ODD decision for a different drug product made nearly 25 years ago*.
- FDA’s prior decision, which was based upon a “cost recovery” analysis for the drug Subutex (buprenorphine sublingual tablets), relied upon inaccurate information and unreasonable assumptions provided by the sponsor, Indivior¹, that turned out to be wildly

¹ Many of the actions described in this petition were performed by Indivior’s predecessors, Reckitt & Colman Pharmaceuticals, Inc. and Reckitt Benckiser Pharmaceuticals. For ease of reference, this petition will refer to all of these entities collectively as “Indivior.”

inaccurate. If reasonable and fair assumptions had been made, Subutex would not have been eligible for ODD in 1994.

- Moreover, because those assumptions were known to be false as early as 2000, two years before Subutex was approved, ODD should have been revoked at that time. In any event, because those assumptions are now known to be false, it would be contrary to the statute, as well as completely irrational, to rely upon them today to award ODD to Sublocade.
- Indivior already received seven years of orphan drug exclusivity (“ODE”) for Subutex; nevertheless, it now appears to be seeking a second, successive ODE period for Sublocade based upon the same ODD and relying on 1994 (inaccurate and non-current) data. Granting ODD or ODE to Sublocade under these circumstances would violate the intent of Congress to provide special incentives only to *bona fide* orphan drugs and to prevent inappropriate evergreening.
- More importantly, granting a period of ODE to Sublocade would have devastating public health consequences by blocking any and all future buprenorphine products from coming to market for 7 years (no earlier than December 2024) – *in the middle of one of the worst opioid epidemics in U.S. history*. This would also result in monopoly pricing. Such an outcome would represent an historic abuse of the Orphan Drug Act.

I. Executive Summary

Prior to 1983, pharmaceutical companies did not routinely invest in research for drugs to treat rare diseases because the patient populations were too small for such drugs to be profitable. The Orphan Drug Act was enacted in 1983 to promote the prompt availability of drugs for rare diseases by providing special incentives to sponsors, such as grants, exemptions from fees and testing requirements, and, most significantly, seven years of exclusive marketing.

To qualify for these incentives, a drug must be intended to treat a “rare disease or condition,” which is most commonly defined as a disease or condition that affects less than 200,000 patients in the United States. In highly unusual circumstances – of which there have been only three instances in the 35 years since the inception of the Orphan Drug Act in 1983 – a drug may qualify if it affects more than 200,000 Americans but there is “no reasonable expectation” the sponsor will recover the costs of developing and marketing the drug.

Sublocade does not qualify as an orphan drug under either prong. First, it is intended for the treatment of OUD, a disease that affects several million patients in the United States. Second, by Indivior’s own admission Sublocade is expected to be highly profitable. Indivior forecasts that net revenues will be in the range of \$50 million to \$70 million for fiscal year 2019, and the company “remains confident” of peak annual net revenue of more than \$1 billion, which would make Sublocade a “blockbuster.” Because the current marketplace already provides adequate incentives for development of Sublocade in terms of huge expected profits, Sublocade is not eligible for the special incentives reserved for *bona fide* orphan drugs.

Sublocade nevertheless has been designated as an orphan drug because of a well-meaning but ultimately harmful administrative policy adopted by FDA. This informal policy allows Sublocade to “piggy-back” on the ODD granted to another drug in 1994 – *nearly 25 years ago*. In essence, FDA considers Sublocade and the other drug, Subutex, to be the “same drug” because they both contain buprenorphine. Accordingly, FDA transferred the ODD granted to Subutex in 1994 to Sublocade nearly 25 years later (without considering the underlying eligibility or appropriateness of Sublocade as an “orphan drug”).

The basis for FDA’s original grant of ODD to Subutex, however, was highly unusual – and highly specific to Subutex and the marketing conditions it expected to face in the mid-1990s. The vast majority of the clinical development program for Subutex was paid for with taxpayer dollars via large grants from the National Institute of Drug Abuse (“NIDA”). Despite this significant government funding, or the fact that FDA had a “significant concern” that the intended patient population was estimated to be between 1,000,000 and 1,500,000 in 1993, FDA nonetheless granted ODD to Subutex based on Indivior’s assertions that there was “no reasonable expectation” it would recover the costs of developing and marketing Subutex during the first seven years after approval. This 1993 assertion, which turned out to be wildly inaccurate, has absolutely no relevance to whether Sublocade, which was approved nearly 25 years later, qualifies as an orphan drug in 2019. By applying the 1994 ODD to Sublocade even though the cost recovery analysis focused solely on Subutex, FDA’s decision not only is arbitrary and capricious, but also violates the statutory provision requiring it to consider all sales of the relevant “drug” in the United States. *See* 21 U.S.C. § 360bb(a)(2)(B).

Moreover, the 1994 designation decision itself was unjustified and unreasonable, as evidenced by the more than \$285 million in sales enjoyed by Indivior since the original approval of Subutex in 2002. This was due, in large part, to the fact that Indivior provided FDA with inaccurate and misleading information. While Indivior was telling FDA that the market for buprenorphine would be severely restricted for the foreseeable future (*i.e.*, limited to use in methadone clinics), the company was making business decisions, including extensive lobbying plans, based upon the expectation that the market for buprenorphine could and would expand significantly within a few years. These plans crystallized in 2000 – two years prior to Subutex’s approval in 2002 – with passage of the Drug Addiction Treatment Act (“DATA 2000”), a law that was drafted by Indivior and enacted with significant lobbying assistance from the company. Accordingly, if reasonable and fair assumptions had been made – assumptions that Indivior itself was relying upon at the time to run its business – Subutex would not have been eligible for ODD in 1994. In any event, it was clear in 2002 when Subutex was approved that the 1994 assumptions were unreasonable, at which time ODD should have been revoked.

In light of this history, Braeburn was dismayed to learn from FDA that Sublocade may be granted ODE, which could prevent any other buprenorphine product intended to treat OUD from coming to market until December 30, 2024. This would be a major mistake not only because Sublocade obviously does not qualify as a *bona fide* orphan drug, but also because *Indivior already obtained and used its ODE for Subutex (and Suboxone) from 2002 through 2009 to generate extraordinary and long-dated financial returns*. Incredibly, Indivior now appears to be seeking a second, successive exclusivity period for Sublocade based upon the same 1994 ODD

that triggered the first exclusivity period for Subutex. This is a blatant attempt to abuse the orphan drug system by engaging in inappropriate and offensive “evergreening” of ODE, contrary to the intent of Congress.

If FDA grants ODE, it would have a devastating impact on the public health, and is completely inconsistent with the well stated goals of FDA and the US Government to expeditiously increase access to a wider range of therapies to address one of the worst public health crises in United States history. According to the Centers for Disease Control and Prevention, almost 400,000 people died from an opioid-related overdose from 1999 to 2017 – nearly 50,000 in 2017 alone – and those numbers are escalating. To combat this crisis, the federal government has recognized that new and better treatment options are needed, especially in relation to increased access, and use, of buprenorphine. For its part, the FDA issued a final guidance document in 2019 to promote the development of innovative treatments for OUD, particularly buprenorphine products that can be administered as long-acting implants or injectable depots.

A decision to grant ODE to Sublocade will completely frustrate these goals by effectively freezing the development of new buprenorphine products for the treatment of OUD – *until approximately 2025*. This is because ODE is broad, preventing FDA from approving not just generic copies of Sublocade, but also *any* product intended for the same use that contains buprenorphine. While sponsors theoretically could avoid exclusivity by making a showing of “clinical superiority,” this showing is unpredictable and often requires expensive head-to-head, comparative clinical trials, thereby fundamentally “lifting the regulatory bar” beyond a showing of safety and effectiveness for any sponsor seeking marketing approval for buprenorphine. As a practical matter, therefore, an award of ODE would effectively strangle investment in innovative OUD treatments containing buprenorphine for the foreseeable future, contrary to the expressed policies of FDA, HHS and the White House. This would severely limit competition and treatment options and result in monopoly pricing for a critical drug needed to fight the opioid epidemic.

FDA, however, has the tools and authority to avoid these consequences. For the reasons discussed below, Sublocade is not now and never has been eligible for ODD. Accordingly, FDA should use its authority to revoke Sublocade’s ODD pursuant to 21 C.F.R. § 316.29(a) and concomitantly refuse to grant, or revoke, ODE. These actions will protect the integrity of the Orphan Drug Act by rejecting transparent evergreening tactics for products that do not qualify as *bona fide* orphan drugs. More importantly, it will maintain robust incentives for companies to invest in new and innovative treatment options for OUD patients to combat the ongoing opioid crisis, consistent with federal objectives. The grounds for this request are set forth in detail below.

II. Actions Requested

For the reasons that follow, Braeburn respectfully requests the Commissioner to:

1. Revoke the orphan drug designation granted to Sublocade (buprenorphine) for treatment of opiate addiction in opiate users (currently referred to as OUD); and
2. Refuse to grant orphan drug exclusivity to Sublocade, or withdraw such exclusivity, if already granted.

III. Statement of Grounds

A. Legal and Factual Background

1. The Orphan Drug Act

The Orphan Drug Act is intended to provide special incentives for the development of drugs intended to treat rare diseases that otherwise would not be developed. These incentives include research grants, tax credits, waived FDA user fees and protocol assistance. *See, e.g.*, 21 U.S.C. § 360ee. In addition, the Orphan Drug Act provides a particularly valuable seven-year period of exclusive marketing, known as Orphan Drug Exclusivity or ODE, for designated orphan drugs that are approved by FDA. *Id.* § 360cc.

To qualify for many of these incentives, a sponsor must request that its drug be “designated” by FDA as a drug for a “rare disease or condition,” *i.e.*, an orphan drug. *Id.* § 360bb. The term “rare disease or condition” is defined by the statute as a disease or condition that:

- affects less than 200,000 patients in the United States (“Patient Population Prong”); or
- affects more than 200,000 but for which there is “no reasonable expectation” that the costs of developing and marketing the drug will be recovered from sales of the drug in the United States (“Cost Recovery Prong”).

Id. § 360bb(a)(2). A request for designation must be submitted to FDA *before* the submission of the application for the proposed orphan drug. *Id.* § 360bb(a)(1). An orphan drug that is both designated and approved is eligible for ODE. *Id.* § 360cc.

In recent years, however, FDA appears to have adopted an informal policy that allows *certain* sponsors to transfer the ODD granted to one drug to a subsequent version of that drug *without* submitting: (a) a separate request for ODD per 21 C.F.R. § 316.20; or (b) a “plausible

hypothesis” of clinical superiority.² This informal policy has been exclusively applied where both the new and prior drug products are sponsored by the same company. In such situations, FDA automatically bestows the ODD that was granted to the first product to any subsequent product that contains the same active moiety and is intended for the same use as the first product (without even the briefest or most cursory re-assessment). FDA has explained that this policy is justified because ODD applies to the active moiety, not a specific drug product.³

Although this policy is briefly mentioned on FDA’s website, it is not set forth or explained in any FDA regulation or guidance document. Moreover, it is unclear when it was adopted, since FDA has applied it in some recent cases (*e.g.*, Orenitram) but not in other older situations (*e.g.*, Nutropin Depot, Tyvaso) (see discussion in section III.B.2 below). The precise scope of FDA’s informal policy, therefore, is unclear. However, it does not seem to incorporate any time limits between ODD transfers. In other words, as far as Braeburn can tell, FDA will transfer ODD regardless of how long ago (or on what basis) the original ODD was granted, and irrespective of any other considerations or intervening developments.

2. Subutex

Subutex is a sublingual tablet formulation of buprenorphine (NDA 20-732) approved on October 8, 2002. It was developed with substantial funding and assistance from the federal government, particularly NIDA. Together with a related product called Suboxone (buprenorphine/naloxone), also approved on October 8, 2002, Subutex was the first buprenorphine drug product approved for “the treatment of opioid dependence.”⁴

Approximately eight years before its approval – on June 15, 1994 – Subutex was designated by FDA as an orphan drug for “opiate addiction in opiate users.”⁵ The designation was unusual because it was based on the Cost Recovery Prong, not the Patient Population Prong. Since 1983, only three drugs appear to have received ODD based upon the Cost Recovery Prong (and two of those are Subutex and Suboxone). As noted above, Subutex could not meet the requirements of the Patient Population Prong because, at the time (early 1990’s), FDA estimated that the number of “opioid addicts” in the United States exceeded one million patients, which is well above the statutory threshold of 200,000 patients.⁶

Accordingly, FDA granted ODD to Subutex based on its determination that there was “no reasonable expectation” that the cost of developing and marketing buprenorphine for “opiate addiction in opiate users” would be recovered from sales of the drug in the United States (FDA

² To obtain ODD for a new version of a drug that contains the same active moiety and is intended for the same use as a previously-approved drug (*i.e.*, is “otherwise the same”), a sponsor must provide a “plausible hypothesis” that the second-in-time drug is clinically superior to the previously approved drug. 21 C.F.R. §§ 316.20(a), 316.25(a)(3).

³ See Def.’s Response to Pl.’s Mot. Summ. J. and Cross-Mot., *United Therapeutics Corp. v. HHS*, Civ. Action No. 17-1577, p. 13 (Dec. 22, 2017) (Exhibit 1).

⁴ See Subutex Prescribing Information, INDICATIONS AND USAGE (2002), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/20732,20733lbl.pdf

⁵ Letter from Marlene Haffner, M.D., M.P.H. to Charles O’Keeffe, Executive Vice President, Reckitt & Colman Pharmaceuticals, Inc. (June 15, 1994) (Exhibit 2).

⁶ FDA ODD Review for Subutex, p. 3 (June 25, 1993) (“1993 ODD Review”) (Exhibit 3).

made the determination despite the fact that NIDA had borne a substantial portion of the development costs). FDA's determination relied upon several important assumptions and limitations. First, the analysis only considered revenue expected to be generated during the first seven years of marketing of Subutex (with an initially estimated approval date of 1995).⁷ Second, it assumed that existing requirements that limited the use of narcotics to certain treatment centers (e.g., methadone clinics) would not be liberalized prior to Subutex's approval or, indeed, during the life of the product. This assumption, in turn, supported assumptions that the pricing options for Subutex and the size of the available patient population likewise would be severely circumscribed.⁸

As discussed further below in section III.B.3, these assumptions were not reasonable when made and, not surprisingly, turned out to be highly inaccurate. This was due, in large part, to enactment of DATA 2000 on October 17, 2000.⁹ DATA 2000 effectively negated all assumptions put forward by Indivior about the limited market for buprenorphine by exempting buprenorphine from the severe restrictions that applied to other narcotics, such as methadone. DATA 2000 thus significantly changed the marketplace for buprenorphine, thereby dramatically improving the financial prospects of Subutex and Indivior's ability to expeditiously earn oversized economic returns (in excess of its investment). Moreover, despite its assertions to FDA that the marketplace restrictions were unlikely to be changed during the life of Subutex, Indivior was instrumental in conceiving and passing DATA 2000 *prior to the approval of Subutex* (see section III.B.3.a below).

Because it was designated as an orphan drug, Subutex was granted a seven-year period of ODE upon its approval in 2002. That exclusivity period expired on October 8, 2009.¹⁰ Because of the changes to the law wrought by DATA 2000, Subutex became an extremely profitable drug for Indivior. Between 2003 and 2007, Subutex prescriptions increased rapidly from approximately 9,000 per year to approximately 192,000 per year, which paralleled equally rapid increases in sales from approximately \$1 million in 2003 to approximately \$42,780,000 in 2007.¹¹ Indeed, during the approximately nine years it was marketed (between 2002 and 2011), Subutex generated net revenue in the United States of over \$285 million.¹² When combined with Suboxone sales, which also received ODD and ODE pursuant to the Cost Recovery Prong, Indivior reported more than \$2.3 billion in net revenue generated from Subutex and Suboxone in the United States, (not including sales from 2002 and 2003).¹³ Together, Subutex and Suboxone became two of Indivior's most profitable products and represent the two largest and most successful products in the history of the treatment of OUD.

⁷ FDA ODD Review for Subutex, p. 4 (June 14, 1994) ("1994 ODD Review") (Exhibit 4).

⁸ 1994 ODD Review, p. 5 ("It is reasonable to assume that there will be virtually no change in the treatment-seeking population, or that any positive shift will be incremental.").

⁹ Pub. L. No. 106-310, § 3501 et seq., 114 Stat. 1101 (2000).

¹⁰ FDA Database, Orphan Drug Designations and Approvals, accessed April 3, 2019 (Exhibit 5).

¹¹ Mark T, Kassed C, et al. Alcohol and Opioid Dependence Medications: Prescription Trends, Overall and by Physician Specialty. Author manuscript published in final edited form as: *Drug Alcohol Depend.* 2009 January 1; 99 (1-3): 345-349. Doi:10.1016/j.drugalcdep.2008.07.018 ("Mark & Kassed Article") (Exhibit 6).

¹² Data on file (derived from Indivior Annual Reports and Symphony Health Solutions Integrated Sales Audits).

¹³ *Id.*

3. Sublocade

Sublocade is an extended-release, injectable depot formulation of buprenorphine approved for “the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of seven days.”¹⁴ When Sublocade is injected into the body, it forms a solid depot that is intended to release buprenorphine over a one-month period. Indivior, the sponsor of Subutex, submitted a 502(b)(2) application for Sublocade (NDA No. 209819) on May 30, 2017, and FDA approved Sublocade six months later on November 30, 2017.

According to FDA’s Orphan Drug Database (“Database”), Sublocade is currently designated as an orphan drug for “[t]reatment of opiate addiction in opiate users.”¹⁵ The Database further states that this designation was granted on June 15, 1994. Since Sublocade did not exist in 1994, Sublocade’s ODD appears to be based on FDA’s original designation of Subutex as an orphan drug in 1994. In other words, FDA appears to have applied the informal policy described above solely because Sublocade and Subutex contain the same active moiety (buprenorphine) and are both owned by Indivior. Based on the information in FDA’s Database, Braeburn does not believe Indivior submitted a separate ODD request for Sublocade.¹⁶ Perhaps most alarmingly (and surprisingly given the obvious changes to the market landscape and the explosion of the opioid crisis), FDA does not appear to have done any assessment to re-confirm that Sublocade is a *bona fide* “orphan drug” that needs or deserves the special incentives under the Orphan Drug Act.

FDA’s publication entitled *Approved Drug Products With Therapeutic Equivalence Codes*, commonly referred to as the Orange Book, currently indicates that Sublocade qualifies for 3-year exclusivity under the FFDCA, with an exclusivity code of “NP” (New Product) that expires on November 30, 2020.¹⁷ Although Sublocade was approved more than 16 months ago, the Orange Book does not indicate that Sublocade has been awarded ODE. Nevertheless, Braeburn has been informed that FDA currently is considering whether or not to award ODE to Sublocade. Under the Orphan Drug Act, Sublocade is not eligible for ODE unless it is “clinically superior” to previously approved buprenorphine drugs. 21 U.S.C. § 360cc(c). Although Braeburn does not believe Sublocade meets this high standard, there is no guarantee that FDA will agree with Braeburn’s analysis.¹⁸

¹⁴ Sublocade Prescribing Information, § 1 (Nov. 2017), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209819s001lbl.pdf.

¹⁵ FDA Database, Orphan Drug Designations and Approvals, accessed April 3, 2019 (Exhibit 5).

¹⁶ Braeburn submitted a Freedom of Information Act (“FOIA”) request for such information and will supplement this Petition if it receives relevant documentation regarding a standalone ODD request for Sublocade.

¹⁷ FDA Electronic Orange Book, Sublocade, accessed April 3, 2019 (Exhibit 7).

¹⁸ Braeburn reserves its right to address “clinical superiority” and similar issues related to ODE in a separate submission to FDA. This Petition does not address three-year exclusivity for Sublocade in any way.

B. FDA Should Revoke Orphan Drug Designation for Sublocade

FDA should not award seven years of exclusive marketing to Sublocade in reliance on a 25-year-old ODD decision that was itself based on inaccurate and potentially misleading information for a different drug product that already received its seven years of ODE and which ultimately generated outsized economic returns for its sponsor. Nor should it award such exclusivity under these circumstances in the middle of one of the worst opioid epidemics in U.S. history. Such an outcome would represent an historic abuse of the Orphan Drug Act.

Not surprisingly, the grant of ODE to Sublocade is not compelled by either the statute or the regulations. On the contrary, FDA has ample authority – and justification – to revoke Sublocade’s ODD and thereby prevent it from obtaining a seven-year exclusivity period it clearly does not deserve.

FDA’s longstanding regulations give the Agency the power to revoke ODD if:

1. the request for designation contained an “untrue statement of material fact;”
2. the request “omitted material information” required by the regulations; or
3. “FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefor.”

21 C.F.R. § 316.29(a). For an ODD based on the Cost Recovery Prong, revocation can be based upon new information collected after the ODD decision – or even after approval – demonstrating that the drug product actually is profitable and thus that the initial economic assumptions were not reasonable.¹⁹ Here, for the reasons described below, FDA has grounds to revoke Sublocade’s ODD based upon all three criteria. Accordingly, FDA should immediately act to revoke the ODD for Sublocade.

1. Sublocade Is Not Eligible for ODD Under the Orphan Drug Act

FDA should revoke ODD because Sublocade is not, and never was, qualified as an orphan drug under the statute. As noted above, the Orphan Drug Act requires a drug to meet one of two criteria to qualify as an orphan drug: the Patient Population Prong or the Cost Recovery Prong. Sublocade does not satisfy the requirements of either prong.

First, Sublocade is intended to treat a disease – OUD – that affects *millions* of patients in the United States. In 1993, FDA estimated that the total number of patients in the United States addicted to opioids was between 1,000,000 and 1,500,000 and thus “easily exceeded” the 200,000 patient threshold required under the statute.²⁰ Since then, the opioid epidemic has been fueled by prescription drug abuse, including oxycodone and fentanyl. In 2014, the Substance Abuse and Mental Health Services Administration (“SAMSHA”) estimated that almost 2.3

¹⁹ See FDA ODD Review for Raloxifene (Evista), p. 13 (May 20, 2005) (recognizing that FDA’s regulations allow revocation based on sales occurring after approval) (Exhibit 8).

²⁰ 1993 ODD Review, p. 3.

million people aged 12 years and older abused or were dependent on opioids, up from almost 1.7 million in 2005.²¹ Accordingly, OUD is certainly not a rare disease, and Sublocade therefore clearly does not satisfy the Patient Population Prong.

Second, Sublocade is expected to be highly profitable. Indivior forecasts that net revenues will be in the range of \$50 million to \$70 million for fiscal year 2019.²² Moreover, the company has consistently reinforced that peak annual net revenue for Sublocade would exceed \$1 billion. As recently as December 18, 2018, Indivior stated that it “remains confident” of this prediction.²³ Based on the company’s own assessment, therefore, Sublocade is expected to be a highly profitable drug that clearly does not satisfy the Cost Recovery Prong.

Despite these conspicuous factual and statutory deficiencies, which confirm that buprenorphine is no longer a *bona fide* orphan drug, FDA nevertheless granted ODD to Sublocade. Although the basis for FDA’s decision is not explained in the Database, given the June 15, 1994 designation date, it appears that FDA is allowing Sublocade to piggy-back on the ODD granted to Subutex approximately 25 years ago. Specifically, FDA appears to be relying on the regulatory fiction that Sublocade is the “same drug” as Subutex (because both contain buprenorphine) and thus that Subutex’s 1994 ODD can be “grandfathered” or otherwise transferred to Sublocade twenty-five years later – without a new ODD request or FDA review under the statutory and regulatory standards.

For the reasons discussed below, FDA’s informal ODD transfer policy cannot be applied to Sublocade. Although such transfers may be consistent with FDA’s general policy of granting ODD “liberally,”²⁴ as applied here, the ODD transfer is unduly liberal and conflicts with the underlying goals of the Orphan Drug Act and the explicit statutory and regulatory requirements applicable to the designation process. As such, Sublocade’s ODD should be revoked.

First, FDA’s ODD “transfer policy” permits the designation of drugs that are not *bona fide* orphan drugs. Congress included a designation process in the Orphan Drug Act specifically “to assure that the financial incentives and other regulatory provisions of the bill apply only to drugs for rare diseases and conditions.”²⁵ Indeed, the primary purpose of the Orphan Drug Act is “to provide incentives to develop promising drugs for rare diseases or conditions *that would not otherwise be developed and approved.*”²⁶ By circumventing the designation process for new versions of previously designated drugs, FDA’s informal policy creates a loophole through which drugs that do not presently satisfy either the Patient Population Prong or the Cost Recovery Prong nevertheless can reap the special benefits of ODD, including the possibility of ODE. In this case, for instance, Sublocade received ODD despite the fact it is expected to be a

²¹ GAO Report, *Opioid Addiction: Laws, Regulations, and Other Factors Can Affect Medication-Assisted Treatment Access*, p. 2 (Sept. 27, 2016) (GAO-16-833), available at <https://www.gao.gov/products/GAO-16-833>.

²² Indivior Financial Results, p. 2 (Feb. 14, 2019) (Exhibit 9).

²³ Indivior Legal and Trading Update, p. 2 (Dec. 18, 2018) (Exhibit 10).

²⁴ See 56 Fed. Reg. 3338, 3340 (Jan. 29, 1991) (“On the whole, FDA would liberally grant orphan-drug designation when the threshold prevalence or profitability tests are met.”).

²⁵ H.R. Rep. No. 97-840, p. 8 (1982).

²⁶ 76 Fed. Reg. 64,868, 64,870 (emphasis added).

blockbuster drug that treats a patient population numbering in the millions. Because market conditions already provide adequate incentives for the development of Sublocade, it should not be eligible for the special incentives reserved for *bona fide* orphan drugs.

Second, FDA's policy facilitates perpetual evergreening of exclusivity. Congress has expressed strong concerns over the years – including in recent years – that companies could abuse the orphan drug system by seeking designation for drugs with significant commercial value “solely to get market exclusivity that would cut off competitors who might also seek approval of the drug.”²⁷ FDA's informal policy exacerbates this problem by permitting infinite, successive seven-year periods of ODE based upon a single ODD determination – even when the subsequent versions of the original drug are highly profitable. Here, for example, Subutex has already enjoyed a seven-year period of ODE together with enormous financial returns beginning in 2002 based on the original ODD granted in 1994. Now, Indivior is seeking a second, successive exclusivity period for Sublocade based upon the same ODD that triggered the first exclusivity period, despite the fact that Sublocade is expected to be a “blockbuster” drug and notwithstanding that the costs incurred to develop buprenorphine over twenty years ago have been recovered many times over. This is a blatant attempt to abuse the orphan drug system by engaging in inappropriate “evergreening” of ODE, contrary to the intent of Congress.

FDA's longstanding policy has been that ODE is “used up” or “spent” if the same drug already has been approved for the same orphan indication.²⁸ FDA thus will not award a second exclusivity period to the same drug, a position Congress recently affirmed when it amended the Orphan Drug Act to include a “clinical superiority” requirement. FDA should apply the same policy to ODD and consider Indivior's 1994 ODD to have been “used up” or “spent” once Subutex's ODE was triggered. As such, it should not be available for “re-use” by Sublocade to seek a second, successive exclusivity period or for evergreening by future drug products.

Third, FDA's informal policy does not constitute “reasoned decision-making” because it allows the Agency to ignore any and all factors *most relevant* to a designation decision, *i.e.*, current information about patient population and cost recovery. This permits an absurd “one-and-done” assessment by FDA on orphan drug *bona fides*, notwithstanding that, as is the case here, more than two decades have passed since the initial designation assessment. In this case, the cost recovery analysis performed in 1994 for Subutex has absolutely no bearing on whether Sublocade (or buprenorphine) meets the relevant statutory requirements to qualify as an orphan drug today.

Worse, the 1994 decision was based upon assumptions about the marketplace that changed radically in 2000 after passage of DATA 2000 – *well before the approval of Subutex*. Those changes made Subutex extremely profitable and, as projected by Indivior, promise to transform Sublocade into a “blockbuster” drug with peak annual revenue exceeding \$1 billion. FDA cannot remain “blind” to this information, or ignore fundamental and obvious marketplace changes, and thereby grant ODD to Sublocade based upon historical data and assumptions that

²⁷ H.R. Rep. No. 100-473, p. 6 (1987).

²⁸ Nutropin Depot (ProLease) ODE Review, p. 2 (June 6, 2000) (Exhibit 11).

are nearly 25 years old and, in hindsight, clearly inaccurate. To do so would be arbitrary and capricious in violation of the Administrative Procedure Act.²⁹ 5 U.S.C. § 706(2)(A).

Fourth, FDA's policy fails to establish reasonable time limits between ODD transfers. Here, FDA is allowing Sublocade to piggy-back on a designation decision that is *almost 25 years old*. There is nothing to prevent similar ODD transfers for drugs approved 50, 100 or even 500 years from now. This is inherently unreasonable and will create ODD "perpetuities" that provide permanent benefits to their holders regardless of whether the future products qualify as *bona fide* orphan drugs. In similar situations, FDA has imposed time limits to prevent a grant of ODD based upon stale and outdated information to drugs that no longer qualify as orphan drugs. See 21 C.F.R. § 316.24(a).³⁰ If FDA included similar time limits (e.g., one year) for transfers of ODD, its policy might be reasonable; in this case, however, the nearly 25-year gap is unreasonable and fails to account for the dramatic marketplace changes - and resultant enormous financial windfalls - that have occurred between 1994 and today (and which clearly negate the appropriateness of providing orphan incentives to any subsequent drugs for ODD).

Finally, FDA's policy violates the statute when applied in the specific context of the Cost Recovery Prong. In making a cost recovery determination, the statute directs FDA to consider "sales in the United States of *such drug*" – without any limitation as to time period. 21 U.S.C. § 360bb(a)(2)(B) (emphasis added). In this case, however, FDA's analysis was limited to the first seven years of expected sales of buprenorphine (*i.e.*, 1995 through 2002) – a time period that could not and did not account for any "sales" of Sublocade.³¹ FDA nevertheless appears to have applied ODD to Sublocade on the grounds that it is the "same drug" as Subutex.

FDA cannot have it both ways. If ODD applies to the "active moiety" broadly, then the statutory cost recovery analysis must be equally broad and account for all reasonably anticipated sales of "such drug," which in this case includes Sublocade. In the alternative, if FDA limits the cost recovery analysis to the first seven years of sales (as it did here in accordance with its regulations),³² then ODD likewise must be limited to the specific "such drug" covered by that assessment (*i.e.*, Subutex). By applying the 1994 ODD broadly to Sublocade even though its cost recovery analysis was focused narrowly on expected sales of Subutex, FDA's decision violates the statutory provision requiring it to consider all "sales in the United States of *such drug*." *Id.* (emphasis added).

²⁹ *Motor Vehicle Mfrs. Assn. of United States, Inc. v. State Farm Mut. Automobile Ins. Co.*, 463 U.S. 29, 43 (1983) (internal citations omitted) (an agency decision is arbitrary and capricious if it "has relied on factors which Congress has not intended it to consider, *entirely failed to consider an important aspect of the problem*, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.") (emphasis added).

³⁰ In that case, FDA has recognized that granting ODD when circumstances change "may be inconsistent with the purpose of the Orphan Drug Act, to provide incentives for the development of drugs for 'rare diseases or conditions ...'" 76 Fed. Reg. 64,868, 64,872 (Oct. 19, 2011). FDA was particularly concerned that ODD could be granted to drugs even if patient prevalence increased beyond 200,000 over time. To minimize this risk, FDA imposed a time limit of one-year for sponsors to respond to ODD deficiency letters.

³¹ 1994 ODD Review, p. 14.

³² 21 C.F.R. § 316.21(c).

2. Sublocade Is Not Eligible for ODD Under the Orphan Drug Regulations

FDA should revoke the ODD for Sublocade for the independent reason that, on information and belief, Indivior never submitted a new request containing a “plausible hypothesis” that Sublocade is superior to previously approved buprenorphine products.³³

Under FDA’s regulations, if a drug is “otherwise the same” as a previously approved drug for the same rare disease or use, the sponsor must present a “plausible hypothesis” that the new drug “may be clinically superior to the first drug.” 21 C.F.R. § 316.20(a). If the sponsor fails to submit a “medically plausible hypothesis for the possible clinical superiority of the subsequent drug,” FDA must refuse to grant ODD. *Id.* § 316.25(a)(3). A drug is considered to be the “same drug” if it contains the same active moiety and is intended for the same orphan indication as the previously approved drug. *Id.* § 316.3(b)(14)(i). This special rule is intended to protect the value of ODE, prevent inappropriate evergreening, and ensure the prompt approval of therapeutically superior drugs.³⁴

In this case, Sublocade is “otherwise the same” as Subutex because both products are single-ingredient buprenorphine drugs intended for the treatment of opiate dependence and addiction, *i.e.*, OUD. Accordingly, under FDA’s regulations, Indivior was required to submit a “plausible hypothesis” of Sublocade’s superiority. *Id.* § 316.20(a). However, on information and belief, Indivior never complied with this requirement and instead obtained ODD by piggybacking on the designation previously granted to Subutex in 1994. Because Sublocade did not satisfy the clear requirements set forth in FDA’s regulations, it was never eligible for ODD.

In accordance with the informal policy described above, FDA appears to have ignored the “plausible hypothesis” requirement for Sublocade because it is the “same drug” as Subutex and thus automatically eligible for ODD.³⁵ But this reasoning is circular: even if Sublocade and Subutex are considered to be the “same drug,” *FDA’s regulations apply to this very situation*. FDA has explained that “[i]n the absence of a clinical superiority hypothesis, the Agency does not interpret the Orphan Drug regulations to permit designation of a drug that is otherwise the same as a drug that is already approved for the same use. ...”³⁶ Put more succinctly, “absent such a hypothesis, designation can be neither sought nor obtained.”³⁷

³³ Braeburn bases this assertion on that fact that FDA identifies June 15, 1994 as the date Sublocade was designated as an orphan drug. This strongly suggests that Indivior did not submit a separate ODD request but instead is relying upon Subutex’s ODD. If Indivior did, in fact, submit a separate ODD request for Sublocade prior to submission of the Sublocade NDA that contained a “plausible hypothesis” of clinical superiority, Braeburn hereby withdraws this argument. Braeburn has submitted a FOIA request for the relevant records on any ODD requests for Sublocade and will update this Petition, if warranted, when we receive a response.

³⁴ FDA Petition Response to CSL Behring, FDA-2011-P-0213, p. 4 (Aug. 8, 2012).

³⁵ As noted above, FDA’s informal policy is mentioned briefly in briefs filed in the UTC case. *See* Def.’s Response to Pl.’s Mot. Summ. J. and Cross-Mot., *United Therapeutics Corp.*, Civ. Action No. 17-1577, p. 13 (Dec. 22, 2017).

³⁶ 78 Fed. Reg. 35,117, 35,122 (June 12, 2013).

³⁷ Letter from Gayatri R. Rao, M.D., J.D., Director, FDA Office of Orphan Products Development, to Philip Katz, Esq., p. 14 (Nov. 13, 2012) (Exhibit 12).

Significantly, the regulations do not distinguish between types of sponsors with respect to this requirement, exempt, or otherwise provide preferential treatment to a sponsor if it developed both drugs at issue. This broad coverage makes sense because the clinical superiority requirement is essential to fostering the overriding goals of the Orphan Drug Act and to preventing evergreening. FDA has explained that if the same drug has already been approved for the orphan disease or condition,

designation would be inappropriate [in the absence of a clinical superiority hypothesis] because it would be inconsistent with the primary purpose of the Orphan Drug Act, which is to provide incentives to develop promising drugs for rare diseases or conditions that would not otherwise be developed.³⁸

In addition, FDA has warned that without a plausible hypothesis of clinical superiority, “permitting orphan-drug designation of a drug that is already approved for the orphan indication could permit inappropriate ‘evergreening’ of exclusive approval periods.”³⁹ Of course, both of these concerns apply with equal force regardless of whether the drugs at issue have been developed by different sponsors or by the same sponsor. Indeed, the example of “inappropriate evergreening” described in the FDA quote above involves a single sponsor.

In the past, FDA has enforced its “clinical superiority” regulation even where the drugs at issue were developed by the same company. For example, FDA required Genentech to provide a plausible hypothesis that Nutropin Depot, a sustained-release formulation of human growth hormone, was clinically superior to Nutropin, Genentech’s previously-approved, immediate-release formulation of human growth hormone.⁴⁰ Likewise, FDA refused to grant ODD to Tyvaso, United Therapeutics Corporation’s (“UTC’s”) inhalation formulation of treprostinil, until the company demonstrated that Tyvaso was clinically superior to Remodulin, the company’s IV formulation of treprostinil.⁴¹ Although FDA appears to have changed its policy in subsequent cases (*e.g.*, Orenitram), Braeburn submits that the above examples followed the proper process and are more consistent with clear regulatory requirements and goals of the Orphan Drug Act than FDA’s new informal policy.

Finally, FDA’s recently-adopted policy is arbitrary and capricious because it treats similarly-situated sponsors differently.⁴² Existing sponsors can receive ODD for new drug products without any showing of clinical superiority or demonstration that the new product still qualifies as an orphan drug. This allows existing sponsors to reap all of the benefits granted to orphan drugs, including exemptions from user fees and pediatric testing requirements, even if

³⁸ 76 Fed. Reg. 64,868, 64,870.

³⁹ *Id.*

⁴⁰ Nutropin Depot (ProLease) ODD Review (Apr. 27, 1999) (Exhibit 13).

⁴¹ Letter from Frank Sasinowski to Timothy Cote, M.D., M.P.H., Director of FDA’s Office of Orphan Products Developments, p. 1 (July 20, 2009) (referencing FDA letter dated May 5, 2009 denying ODD for Tyvaso because it had not presented a plausible hypothesis of clinical superiority) (Exhibit 14).

⁴² *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C. 1997) (recognizing that unjustified differential regulatory treatment of materially identical products is arbitrary and capricious).

their new products do not independently qualify as orphan drugs at the time of subsequent approval. This, in fact, is what happened with Orenitram (treprostinil) extended-release tablets, which was designated as an orphan drug without being required to (a) submit a new designation request, (b) satisfy the Patient Population or Cost Recovery Prongs, or (c) demonstrate a plausible hypothesis of clinical superiority, but nevertheless was exempted from pediatric testing requirements.⁴³

New sponsors, by contrast, must meet all statutory and regulatory requirements for ODD at the time of the request, including the Patient Population/Cost Recovery requirements and the “plausible hypothesis of clinical superiority” requirement. If they fail to satisfy applicable requirements, they are not eligible for the special incentives and exemptions available to designated orphan drugs, unlike similarly situated drugs subject to FDA’s informal policy. This disparate treatment is unjustified and prejudicial.

3. Subutex Was Not Eligible For ODD In 1994 or 2002

Even if Sublocade is permitted to rely upon the 1994 ODD decision for Subutex, Sublocade’s ODD nevertheless must be revoked because *Subutex* was not eligible for ODD in 1994. Moreover, Subutex’s designation should have been revoked prior to 2002 based upon known legal and marketplace changes, including passage of DATA 2000, which demonstrated that the assumptions underlying the original ODD request and decision were invalid and inaccurate. In short, Subutex was never eligible for ODD because there was always a “reasonable expectation” that it would recover its costs, and this is clearly supported by the outsize economic returns accruing following approval.

a. The 1994 ODD Was Based Upon Inaccurate Information and Unreasonable Assumptions Provided By Indivior

Indivior submitted its request for ODD in 1993.⁴⁴ This submission, however, was filled with inaccurate information and unreasonable assumptions about cost recovery for Subutex. For example, Indivior asserted that Subutex would be approved in 1995.⁴⁵ This, however, was an obvious impossibility given that “the IND’s had just been submitted in May, 1994, the CRADA has just been formally agreed with NIDA, and 1994 is half over ...”⁴⁶ The 505(b)(2) application for Subutex, in fact, was not submitted to FDA until March 28, 1997, and was not approved by FDA until 2002 – seven years after Indivior’s prediction. By that time, the marketplace for buprenorphine had changed dramatically.

Indeed, the marketplace for buprenorphine factored heavily in Indivior’s 1993 assumptions and hypotheses regarding cost recovery. At the time, products such as methadone

⁴³ Orenitram Approval Letter, p. 2 (Dec. 20, 2013) (exempting Orenitram from pediatric testing requirements because of ODD status) (Exhibit 15).

⁴⁴ Subutex ODD Request (Nov. 17, 1993) (Exhibit 16).

⁴⁵ 1994 ODD Review, p. 3 (sponsor’s submission “included the assumption that the product would be first marketed in 1995.”).

⁴⁶ 1994 ODD Review, p.4.

and levomethadyl acetate (“LAAM”) were subject to significant regulatory oversight by both FDA and the Drug Enforcement Administration (“DEA”) and generally restricted to use in a closed system of approved clinics and hospital pharmacies, commonly known as “methadone clinics.”⁴⁷ In setting forth its cost recovery analysis, Indivior claimed that buprenorphine would only compete with methadone and LAAM within this closed system. It specifically informed FDA that:

- The number of available “treatment slots” was a maximum of 115,000 nationally;
- There were 104,000 patients already being treated in methadone treatment programs, and thus those programs were close to capacity;
- Buprenorphine does not equate to higher dosage levels of methadone, substantially reducing the number of patients who are suitable for or willing to be treated with it;
- Buprenorphine will compete in the same marketplace with methadone and LAAM and is unlikely to achieve any market share at normal margin price (and increasing price would trigger lower market penetration); and
- Subutex would not recover its research and development costs based on expected sales during the first seven years of marketing.⁴⁸

To underscore these points, Indivior represented to FDA that the limitations on treatment slots for narcotics (and thus the number of eligible patients) were “highly unlikely to be modified during the life of the product.”⁴⁹

However, at the same time Indivior was telling FDA that legal and marketplace changes for buprenorphine were “highly unlikely,” the company was making business decisions based upon the opposite assumption – that such changes “certainly seemed achievable” within five years,⁵⁰ well within the life of the product (and, ultimately, well prior to the actual approval of Subutex in 2002). According to Charles O’Keeffe, Executive Vice President of Indivior’s pharmaceutical business at the time, Indivior undertook the development of Subutex (and Suboxone) only because “[i]t seemed possible that, under the right circumstances and once approved by the FDA for use in treatment of opioid dependence, buprenorphine might be exempted from some of the burdens associated with the use of methadone and LAAM.”⁵¹ Indivior’s business plan – which it viewed as “at least a 5-year project” – involved three connected objectives: (a) obtaining ODE, (b) obtaining FDA approval, and (c) changing the laws

⁴⁷ See generally J. Jaffe, C. O’Keeffe, From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States. *Drug and Alcohol Dependence*. 70: S3-S11 (2003) (“O’Keeffe Article”) (Exhibit 17).

⁴⁸ Subutex ODD Request, p. 2.

⁴⁹ *Id.*

⁵⁰ O’Keeffe Article, pp. S7-S8 (Exhibit 17).

⁵¹ *Id.* at S7.

so that buprenorphine would “reach the mainstream practice of medicine.”⁵² Significantly, Indivior viewed its “legislative effort” to be “inextricably intertwined” with its efforts to obtain FDA approval of Subutex.⁵³ The available evidence thus strongly suggests that Indivior knew the assumptions it was providing to FDA in 1993 and 1994 were highly inaccurate.

Indivior began its lobbying efforts per its business plan at least as early as 1995, drafting a bill that was a precursor to DATA 2000.⁵⁴ Over the next several years, Indivior engaged in extensive lobbying activities to change the legal requirements governing distribution and use of buprenorphine for treatment of opioid addiction.⁵⁵ As expected, those lobbying efforts bore fruit in 2000 with passage of DATA 2000. This was not only roughly within the 5-year window predicted by Indivior but, more significantly, *two years prior to approval of Subutex*.

DATA 2000 dramatically changed the “economics of marketing buprenorphine,” the benefits of which have largely and exclusively accrued to Indivior in the interim. The Act expanded access to addiction treatment for non-methadone scheduled III, IV and V controlled substances, of which buprenorphine was the only product in development for OUD. The Act also created the “DATA 2000 waiver,” which expanded capacity for addiction treatment beyond the “methadone treatment slots” of the narcotic treatment programs to any healthcare practitioner willing to become accredited through an 8-hour educational course. The result of DATA 2000 was the creation of a separate market for OUD treatment known as Outpatient Based Opioid Treatment (“OBOTs”). These OBOTs were not permitted to prescribe methadone and thus had only two FDA approved medications for the treatment of OUD at their disposal: Subutex and Suboxone, both with orphan-protection for 7 years (and both owned by Indivior).

DATA 2000 thus eradicated all assumptions underlying Indivior’s claim that there was “no reasonable expectation” it would recover its costs for Subutex. In particular, it rapidly expanded the capacity of OUD treatment to approximately 348,530 available treatment slots in five years (2007) with DATA 2000 waived healthcare practitioners (3,311 and 2,492 healthcare practitioners, certified for 30 and 100 patients, respectively).⁵⁶ And because these DATA 2000-waivered healthcare practitioners did not have authority to prescribe methadone, Subutex and Suboxone were neither tethered to methadone’s “high doses” nor its low price.

The results were highly profitable for Indivior: between 2003 and 2007, Subutex sales in the U.S. increased substantially from approximately \$1 million in 2003 to approximately \$42,780,000 in 2007.⁵⁷ During the approximately nine years it was marketed (between 2002 and 2011), Subutex generated net revenue in the United States of over \$285 million.⁵⁸ When

⁵² *Id.*

⁵³ *Id.*

⁵⁴ *Id.* at S8.

⁵⁵ *Id.*

⁵⁶ Estimates based on data provide by SAMSHA, Number of DATA-Waived Practitioners Newly Certified Per Year, available at <https://www.samhsa.gov/medication-assisted-treatment/practitioner-program-data/certified-practitioners>.

⁵⁷ Mark & Kassed Article, see supra note 12.

⁵⁸ Data on file (derived from Indivior Annual Reports and Symphony Health Solutions Integrated Sales Audits).

combined with Suboxone sales, Indivior reported more than \$2.3 billion in net revenue generated from Subutex and Suboxone in the United States, (excluding sales from 2002 and 2003, which were not reported in Indivior’s annual reports to shareholders).⁵⁹ This ultimately enabled a broader buprenorphine sales platform within OUD that has accrued to Indivior’s exclusive benefit with billions in sales over nearly two decades.

Braeburn is not suggesting that there is anything wrong with Indivior’s lobbying efforts; on the contrary, they significantly benefited OUD patients by expanding treatment opportunities for buprenorphine. But Indivior’s plans to expand and liberalize the buprenorphine marketplace through lobbying and other activities – and its views that such regulatory changes were achievable – should have been communicated to FDA because they were material to FDA’s cost recovery analysis for purposes of ODD. Indeed, disclosure to FDA of such factors that would obviously “affect the orphan drug status” is mandatory under the annual reporting regulations. 21 C.F.R. § 316.30(c). Instead, Indivior was communicating certain assumptions to FDA (which FDA relied upon) while operating its business on very different assumptions.

Indivior’s initial request for ODD thus contained an “untrue statement of material fact” regarding the likelihood of regulatory changes affecting the marketplace for buprenorphine or, at the very least, “omitted material information” regarding such changes. *See* 21 C.F.R. § 316.29. Moreover, it clearly was based upon inaccurate information and unreasonable assumptions and thus failed justify ODD at the time.

b. Subutex’s ODD Should Have Been Revoked After Enactment of DATA 2000

Moreover, Subutex’s designation should have been revoked once it became clear in 2000 that the assumptions underlying the ODD request were unreasonable and the Cost Recovery Prong was no longer satisfied. But even after passage of DATA 2000, Indivior continued to represent to FDA in annual reports that “[w]e are not aware of any change in the development or marketing plans that will affect the orphan status of either [Subutex or Suboxone].”⁶⁰ Braeburn has identified at least three such submissions in November 13, 2000, January 4, 2002, and October 14, 2002. Contrary to Indivior’s representations, DATA 2000 obviously and radically changed the “marketing plans” for Subutex and Suboxone by expanding the available patient population, protecting buprenorphine from competition from methadone and LAAM, and giving Indivior more control over pricing.

These misrepresentations to FDA’s Office of Orphan Drug Products (“OODP”) in 2000 and 2002 were material because FDA could have revoked the 1994 ODD based upon subsequent legal and marketplace developments, particularly given the enactment of DATA 2000. For this reason, FDA’s annual report regulations specifically require sponsors to report “any changes that may affect the orphan-drug status of the product.” 21 C.F.R. § 316.30(c). While FDA’s regulations explicitly state that changes to the size of the relevant patient population cannot

⁵⁹ *Id.*

⁶⁰ Subutex Orphan Drug Annual Report (Nov. 6, 2000); Subutex Orphan Drug Annual Report (Jan. 4, 2002) (collectively included as Exhibit 18).

trigger revocation, they provide no similar exemption for changes affecting the Cost Recovery Prong. *Id.* § 316.29(c). Accordingly, FDA has reserved the right to revoke ODD if subsequent legal and/or marketplace developments indicate that prior cost recovery assumptions were faulty and/or that there is, in fact, a “reasonable expectation” that a sponsor will recover its costs.

FDA, in fact, stated this proposition explicitly in its ODD decision for raloxifene (Evista), the only other drug designated under the Cost Recover Prong besides Subutex and Suboxone. In that case, FDA required the sponsor to provide FDA with updated information in annual reports – *even after approval* – to “substantiate the assumptions and hypotheses” underlying the initial cost recovery analysis (such as new patents or competitor launches). FDA stated that this additional information was necessary “to determine if the designation and/or marketing exclusivity should remain in place or *whether the designation and/or exclusivity should be revoked as permitted under 21 CFR 316.29.*”⁶¹ Assessing the ongoing applicability of orphan drug status is therefore both a responsibility of FDA and, perhaps more importantly, a reminder that the incentives that are available under the Orphan Drug Act should only be afforded to drug products that are themselves *bona fide* orphan drugs (without reference to earlier drugs or outdated assumptions).

Here, it is clear that the assumptions and hypotheses underlying the 1994 ODD request were inaccurate and unreasonable. There is also evidence that Indivior knew such information was inaccurate but presented it to FDA anyway. If accurate and reasonable assumptions had been made, Indivior could not have shown that there was “no reasonable expectation” it would recover its costs. Accordingly, Indivior was not in fact eligible for ODD for Subutex at the time of the initial request. Moreover, once the legal and marketplace conditions changed after enactment of DATA 2000, Indivior should have informed FDA of this development, and FDA should have revoked Subutex’s ODD. For the foregoing reasons, the 1994 ODD for buprenorphine should be revoked now.

C. FDA Should Refuse to Grant ODE to Sublocade (Or Withdraw Such Exclusivity If Previously Granted)

If FDA revokes ODD for Sublocade or Subutex, it should refuse to grant ODE to Sublocade or withdraw such exclusivity if already granted. Under the statute, ODE cannot be granted to a drug unless it has a valid orphan-drug designation. 21 U.S.C. § 360cc(a) (ODE available for “a drug designated under section 526 for a rare disease or condition”). Likewise, FDA regulations provide that, for an approved drug like Sublocade, “revocation of orphan-drug designation also suspends or withdraws the sponsor’s exclusive marketing rights for the drug ...” 21 C.F.R. § 316.29(b).

⁶¹ FDA ODD Review for Raloxifene (Evista), p. 13 (emphasis added).

1. The United States Is In the Midst of An Opioid Epidemic

Moreover, granting ODE to Sublocade would have a devastating impact on the public health. The United States is in the midst of one of the worst public health crises in its history. According to the Centers for Disease Control and Prevention, almost 400,000 people died from an opioid-related overdose from 1999 to 2017.⁶² Opioid overdose deaths are projected to result in 700,000 deaths during the period from 2016 to 2025.⁶³ In 2017 alone, more than 70,200 people died of a drug overdose, with more than two-thirds of those fatalities—around 68%—attributable to opioid abuse.⁶⁴ Troublingly, these numbers are on the rise: in 2017, the number of opioid-related deaths was six times higher than the number in 1999. *Id.* Recent data suggest that more than two million Americans currently suffer from opioid-related substance-use disorders.⁶⁵

The federal government has recognized this escalating crisis and has made addressing the opioid epidemic in America a top priority. On October 26, 2017, the President declared the opioid crisis a Nationwide Public Health Emergency, “mobilizing his entire Administration to address drug addiction and opioid abuse.”⁶⁶ Likewise, on October 5, 2017, officials from HHS and FDA testified before Congress and reiterated the administration’s commitment to addressing the crisis.⁶⁷ And as part of its five-point strategy to address the opioid epidemic, HHS has pledged to “[i]mprove access to prevention, treatment, and recovery support services to prevent the health, social, and economic consequences associated with opioid addiction and to enable individuals to achieve long-term recovery.”⁶⁸

Consistent with that effort, FDA Commissioner Gottlieb announced in September 2017 that medication-assisted treatment—*i.e.*, the use of medication in combination with counseling and behavioral therapy—“is one of the major pillars of the federal response to the opioid epidemic in this country.”⁶⁹ On October 25, 2017, during a House hearing on the federal response to the opioid epidemic, Dr. Gottlieb went even further, calling for the expanded use of medication-assisted treatment and explaining that FDA would issue new guidance to manufacturers to promote the development of novel therapies, including ones that treat a wider range of symptoms.⁷⁰ FDA issued its final guidance on February 6, 2019.⁷¹

⁶² Centers for Disease Control & Prevention, *Opioid Overdose: Understanding the Epidemic* (Dec. 19, 2018), <https://bit.ly/2jEOHfs>.

⁶³ Q. Chen et al., *Prevention of Prescription Opioid Misuse and Projected Overdose Deaths in the United States*, JAMA Network Open (Feb. 1, 2019), <https://bit.ly/2Gr3Krp>.

⁶⁴ *Id.*

⁶⁵ National Inst. on Drug Abuse, *Opioid Overdose Crisis* (Mar. 2018), <https://bit.ly/2j6YEE1>.

⁶⁶ The White House, Press Release, *President Donald J. Trump Is Taking Action on Drug Addiction and the Opioid Crisis* (Oct. 26, 2017), <https://bit.ly/2VBqPfU>.

⁶⁷ See S. Comm. on Health, Education, Labor and Pensions, *The Federal Response to the Opioid Crisis: Written Testimony on Behalf of Witnesses from HHS* (Oct. 5, 2017), <https://bit.ly/2RHrPjv>.

⁶⁸ HHS, *Strategy to Combat Opioid Abuse, Misuse, and Overdose* at 3, <https://bit.ly/2R5bhPv>.

⁶⁹ FDA, Press Release, *Statement from FDA Commissioner Scott Gottlieb, M.D., on the Agency’s Continued Efforts to Promote the Safe Adoption of Medication-Assisted Treatment for Opioid Addiction* (Sept. 20, 2017), <https://bit.ly/2D02WZr>.

⁷⁰ FDA, Press Release, *Remarks from FDA Commissioner Scott Gottlieb, M.D., as Prepared for Oral Testimony Before the House Committee on Energy and Commerce* (Oct. 25, 2017), <https://bit.ly/2FjVxFp>.

2. Granting ODE to Sublocade Would Choke Off All Future Investment In New Buprenorphine Drugs for OUD

A decision to grant ODE to Sublocade would completely subvert the federal government's response to the opioid crisis by suffocating future investment in new buprenorphine therapies for the treatment of OUD – *until approximately 2025*. The seven-year period of orphan exclusivity is extremely broad, blocking approval not just of Abbreviated New Drug Applications (“ANDAs”), but also of 505(b)(2) applications and full NDAs – *even for novel products that develop all of their own data*. 21 U.S.C. § 360cc(a). This means that ODE would prevent FDA from approving not just generic copies of Sublocade, or even just buprenorphine depot products generally; rather ODE would prevent FDA from approving *any product* intended for the same use that contains buprenorphine, regardless of dosage form, route of administration or technological features.

Indeed, in a recent example, FDA withdrew approval of drugs in a different dosage form than the drug with ODE simply because they all contained the same active moiety and were intended for the same use. FDA explained that “the scope of Bendeka’s *exclusivity extends to all applications containing the same active moiety* as Bendeka, bendamustine, and bars approval of any application containing bendamustine for any exclusivity-protected indication starting on the date of Bendeka’s approval for seven years.”⁷² It is thus clear that the scope of ODE for Sublocade will be expansive.

While a sponsor theoretically could avoid exclusivity by demonstrating that its new buprenorphine product is “clinical superiority” to Sublocade, few, if any, will accept this challenge. FDA’s “clinical superiority” determinations are highly discretionary and thus inherently unpredictable. Moreover, FDA often requires expensive head-to-head, comparative clinical trials. This raises the bar significantly beyond what would be required to demonstrate safety and efficacy. As a practical matter, therefore, an award of ODE would effectively strangle investment in innovative OUD treatments containing buprenorphine for the foreseeable future, contrary to the expressed policies of FDA, HHS and the White House. By suppressing competition unduly, it also will allow Indivior to charge monopoly prices for Sublocade. Because of buprenorphine’s central role in combatting the raging opioid epidemic, this will have a devastating impact on the public health.

D. Conclusion

For the reasons discussed above, Sublocade is not now and never has been eligible for ODD. Accordingly, FDA should use its authority to revoke Sublocade’s ODD pursuant to 21 C.F.R. § 316.29(a) and, concomitantly, refuse to grant, or revoke, ODE. These actions will protect the integrity of the Orphan Drug Act by rejecting transparent evergreening tactics for

⁷¹ See FDA, *Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment—Guidance for Industry* (Feb. 2019), <https://bit.ly/2F3Dmzo> (“2019 OUD Guidance”).

⁷² FDA Letter to Applicants for Certain Products Containing Bendamustine, FDA-2018-N-3773, p. 1 (Feb. 20, 2019).

products that do not qualify as *bona fide* orphan drugs. More importantly, they will maintain robust incentives for companies to invest in new and innovative treatment options for OUD patients to combat the ongoing opioid crisis.

IV. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. §§ 25.30 and 25.31.

V. Economic Impact

Petitioner will submit economic information upon request of the Commissioner.

VI. Certifications

A. Certification under 21 C.F.R. § 10.30⁷³

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,



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⁷³ Braeburn is not submitting the certification set forth in 21 C.F.R. § 10.31(c) because the action requested in this petition, if taken, could not delay approval of any ANDAs, 505(b)(2) applications or 351(k) applications. *See* 21 C.F.R. § 10.31(a)(1). Braeburn, in fact, believes granting this petition would have the opposite effect.

EXHIBIT 1

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

UNITED THERAPEUTICS CORP.,

Plaintiff,

v.

UNITED STATES DEPARTMENT OF
HEALTH AND HUMAN SERVICES *et al.*,

Defendants.

Civil Action No. 1:17-cv-01577

Judge Ellen S. Huvelle

**MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS' RESPONSE TO
PLAINTIFF'S MOTION FOR SUMMARY JUDGMENT AND CROSS-MOTION**

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INTRODUCTION

United Therapeutics Corporation (UTC) asks the Court to grant seven years of market exclusivity for Orenitram (oral treprostinil)—a drug UTC developed to treat a rare disease called pulmonary arterial hypertension. What UTC fails to mention is that Orenitram is merely the latest in a line of such drugs. Prior to Orenitram, UTC developed two other drugs for the same purpose, using the same active ingredient (treprostinil). Each of those drugs received its *own* seven years of exclusivity. The first drug, Remodulin (intravenous and subcutaneous treprostinil) received exclusivity because it was the first drug of its kind; the second, Tyvaso (inhaled treprostinil), because it was shown to be clinically superior to the first. Orenitram is not the first, nor is it clinically superior. Yet UTC nevertheless claims that developing the drug entitles it to extend its fourteen-year monopoly on treprostinil drugs to twenty-one years. This desire for monopoly is understandable: UTC stands to reap tremendous profits if it can continue to exclude potential competitors from the market. But, contrary to what UTC argues, such a monopoly is *not* compelled by the Orphan Drug Act—and not justified given the facts of this case.

The Orphan Drug Act, 21 U.S.C. §§ 360aa *et seq.*, provides for seven years of exclusivity to drugs that the Food and Drug Administration (FDA) has designated and approved for the treatment of rare diseases or conditions. However, the statute does not specify what happens after the expiration of a drug's exclusivity—nor does it indicate whether that exclusivity can be renewed simply by re-formulating an existing drug. There are good reasons to believe that exclusivity should *not* be renewable. In enacting the Orphan Drug Act, Congress sought to incentivize meaningful advances in drug development for previously untreated rare diseases by awarding these developments with, among other things, a seven-year exclusivity period.

Congress never intended to reward companies with serial (and potentially indefinite) periods of exclusivity for minor variations to an already approved drug.

Consistent with the statute's purpose, FDA has, for more than twenty-five years, interpreted the Orphan Drug Act to confer a seven-year period of exclusivity to only the *first* drug approved as an orphan drug (meaning a drug with a new active ingredient or that is clinically superior). This interpretation is both reasonable and deserving of deference. Indeed, Congress recently affirmed this interpretation in enacting the FDA Reauthorization Act of 2017.¹ Under this interpretation, UTC is not entitled to continue its monopoly, because Orenitram is neither novel nor clinically superior to the previously-approved versions of treprostinil. Orenitram should be denied exclusivity, as FDA correctly decided. An alternative result would be anathema to the Orphan Drug Act's underlying purpose, and would create a windfall for UTC to the detriment of patients with a rare disease.

Accordingly, we respectfully request that the Court sustain FDA's decision, and enter judgment in favor of the United States.

BACKGROUND

I. STATUTORY AND REGULATORY FRAMEWORK

A. Drug Approval Process

Under the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. §§ 301 *et seq.*, pharmaceutical companies seeking to market an initial version of a drug must first obtain FDA approval by filing a new drug application (NDA) containing extensive scientific clinical data demonstrating the safety and effectiveness of the drug. *See* 21 U.S.C. § 355(a), (b), (c).

¹ Congress recently enacted the FDA Reauthorization Act of 2017, Pub. L. No. 11-52, 131 Stat. 1005, which, among other things, amends the exclusivity provision of the Orphan Drug Act, 21 U.S.C. § 360cc. Unless otherwise noted, references to 21 U.S.C. § 360cc are to the statute at the time UTC sought orphan drug exclusivity for Orenitram.

Sponsors of NDAs may be able to delay approval of other applications for the same drug by obtaining and listing patents and qualifying for statutory bars on FDA approval (*i.e.*, exclusivities).

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments) amended the Act to add, among other provisions, 21 U.S.C. § 355(b)(2) and 21 U.S.C. § 355(j), which provide abbreviated pathways for new drug approval. 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. *See* H.R. Rep. 98-857, at 14 (June 21, 1984) [FDA 1716].² FDA approves drug applications submitted pursuant to 21 U.S.C. § 355(b)(2) and 355(j), when they have met all requirements for approval and any applicable patent and exclusivity periods have expired or have otherwise ceased to be a barrier.

B. Orphan Drug Act and Related Regulations

In 1983, one year before the passage of the Hatch-Waxman Amendments, Congress enacted the Orphan Drug Act to provide incentives to develop “orphan drugs” for the treatment of “rare diseases and conditions.” *See* H.R. Rep. 97-840, Pt. 1, at 5 (Sept. 17, 1982) [FDA 1695].³ These incentives include tax credits for clinical testing, exemption from application user fees, and the possibility of seven years of orphan drug exclusivity. *See* H.R. Rep. 97-840, Pt. 1, at 5 [FDA 1695]; 21 U.S.C. §§ 360ee, 379h(a)(1)(F); 26 U.S.C. § 45C. Without these incentives, rare diseases and conditions “affect such a small number of persons that there is

² “[FDA ___]” refers to the corresponding page in the administrative record filed in this case.

³ Congress explained that drugs for rare diseases or conditions are “commonly referred to as ‘orphan drugs’” because “[t]hey generally lack a sponsor to undertake the necessary research and development activities to attain their approval by the [FDA].” H.R. Rep. 97-840, Pt. 1, at 6 [FDA 1696].

virtually no commercial value to any drug which is useful against them,” and sponsors have no incentive to support research and drug approval in these circumstances. H.R. Rep. 97-840, Pt. 1, at 6 [FDA 1696]; *see also* 21 U.S.C. § 360bb(a)(2) (defining “rare disease or condition” as a disease or condition affecting fewer than 200,000 in the United States).

1. Orphan Drug Designation

To obtain many of these incentives, sponsors of drugs for rare diseases must first seek and obtain “designation” for their drugs under 21 U.S.C. § 360bb. *See also* 21 C.F.R. §§ 316.31, 316.34 (2011).⁴ The sponsor must submit to FDA a request for designation that includes, among other things, a “description of the rare disease or condition for which the drug is being or will be investigated, the proposed use of the drug, and the reasons why such therapy is needed.” 21 C.F.R. § 316.20(b)(3); *see generally* 21 C.F.R. §§ 316.20, 316.21.

If a drug is the same as “an already approved drug” for the same use (*i.e.*, the drugs contain the same active moiety),⁵ the sponsor must include in the designation request “a plausible hypothesis that its drug may be clinically superior to the first drug.” 21 C.F.R. § 316.20(a), (b)(5). Under this framework, a sponsor is able to secure the benefits of designation—such as tax credits for clinical testing, which help defray the costs of development at an early stage of the process—by presenting a *plausible hypothesis* of clinical superiority, but without having to *demonstrate* clinical superiority before testing is complete.

⁴ Because this version of the regulations was in effect when UTC first requested designation, it is the one applicable to this case. Unless otherwise noted, references to the Code of Federal Regulations are to this version of the regulation.

⁵ The term “active moiety,” as defined in 21 C.F.R. § 316.3(b)(2), means the portion of the drug that is likely responsible for the activity of the molecule, and ignores certain parts of the molecule that generally result in clinically insignificant changes to its chemical structure (such as salt and ester bonds). It is undisputed that the drugs at issue here contain the same active moiety (*i.e.*, treprostinil).

2. Orphan Drug Exclusivity

One of the major incentives in the Orphan Drug Act, and the provision at issue here, is orphan drug exclusivity. Before Congress's recent amendment to the exclusivity provision of the Orphan Drug Act, the statute stated in relevant part:

Protection for drugs for rare diseases or conditions

(a) Exclusive approval, certification, or license
Except as provided in subsection (b), if the Secretary—

(1) approves an application filed pursuant to section 355 of this title, or

(2) issues a license under section 262 of title 42

for a drug designated under section 360bb of this title for a rare disease or condition, the Secretary may not approve another application under section 355 of this title or issue another license under section 262 of title 42 *for such drug* for such disease or condition for a person who is not the holder of such approved application or of such license until the *expiration* of seven years from the date of the approval of the approved application or the issuance of the license.

21 U.S.C. § 360cc(a) (emphasis added). Under this provision, FDA will generally recognize seven years of exclusivity for drugs with orphan designations upon approval of those drugs for those indications within the designated disease or condition. *Id.* During this exclusivity period, FDA will not approve any other application for the same drug for the same indication.

The statute does not specify whether there may be multiple exclusivity periods for a particular drug. Rather, Congress refers only to an approved drug and subsequent “such drug” without further definition. 21 U.S.C. § 360cc; *see also* Orphan Drug Regulations, 57 Fed. Reg. 62,076, 62,078 (Dec. 29, 1992) (noting that Congress left it to FDA to define “such drug”) [FDA 1793]; *Baker Norton Pharm., Inc. v. U.S. Food & Drug Admin.*, 132 F. Supp. 2d 30, 36 (D.D.C. 2001) (“Given the multiple definitions of the term ‘drug,’ and the differing purposes that various

statutory provisions can serve, the Court cannot find that the definition of ‘drug’ in § 360cc(a) is clear and unambiguous.”). Nor does the statute describe the implications of the “expiration” of an orphan drug’s exclusivity. The issue, then, is how the terms “such drug” and “expiration” should be interpreted to effect the statute’s purpose.

After extensive consideration of the Orphan Drug Act’s text and purpose, FDA issued a final rule in 1992 to implement its interpretation of the designation and exclusivity provisions of the Orphan Drug Act.⁶ *See generally* 57 Fed. Reg. 62,076 [FDA 1791]. Among other things, the 1992 regulations describe the rules that apply when a sponsor of a subsequent version of a drug seeks designation and exclusivity for the same indication as a previously approved drug. While the sponsor at the designation stage need only present a plausible hypothesis of clinical superiority, it needs to *demonstrate* such superiority at the approval stage to qualify for seven-year orphan drug exclusivity.⁷

Specifically, under this “clinical superiority” framework, if a sponsor seeks to market a new version of an already approved drug for the same use (even one sharing the same chemical structure), it must demonstrate that the new version is clinically superior to the previously approved drug to avoid being the same “such drug” and potentially blocked by the already approved drug’s exclusivity period. *See* 21 C.F.R. § 316.3(b)(13) (defining “same drug” and excluding a “clinically superior” drug from that definition). This regulatory framework ensures that there will not be serial, potentially infinite, seven-year periods of orphan drug exclusivity for

⁶ The 1992 regulations, which were in effect when UTC initially sought orphan drug designation for Orenitram, apply here. FDA amended its orphan drug regulations in 2013 to further clarify its long-standing view that this framework requires sponsors of subsequent versions of a drug to demonstrate clinical superiority over a previously approved drug to obtain exclusivity. *See generally* 78 Fed. Reg. at 35,132 [FDA 1835].

⁷ Demonstrating clinical superiority is a more rigorous showing than the plausible hypothesis of clinical superiority required at the designation stage. *See* 21 C.F.R. § 316.3(b)(3) (“Clinically superior means that a drug is shown to provide a significant therapeutic advantage”).

the “same” drug (*i.e.*, a drug that has the same active moiety and is approved for the same indication as a previously approved drug, but has not been shown to be clinically superior).

A sponsor may demonstrate clinical superiority by showing that, as compared to the previously approved drug, its drug provides a “significant therapeutic advantage” by providing greater effectiveness or safety, or otherwise makes a “major contribution to patient care.” 21 C.F.R. § 316.3(b)(3). To show greater safety or effectiveness, sponsors may need to present evidence in the form of direct comparative clinical trials. *See id.* § 316.3(b)(3)(i), (b)(3)(ii). A finding that a drug makes a major contribution to patient care is reserved for “unusual cases.” *Id.* § 316.3(b)(3)(iii); *see also* Proposed Rule: Orphan Drug Regulations, 56 Fed. Reg. 3338, 3343 (Jan. 29, 1991) (characterizing major contribution to patient care as a “narrow category”) [FDA 1782]. FDA expressed particular concern that this standard “is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated.” 57 Fed. Reg. at 62,077 [FDA 1792]. The final determination of clinical superiority is made on a case-by-case basis. *See id.* at 62,079 [FDA 1794].

C. The Depomed Decision

In 2013, Depomed, Inc. challenged the clinical superiority framework after its drug Gralise (gabapentin) did not qualify for orphan drug exclusivity. *See Depomed, Inc. v. U.S. Dep’t of Health & Human Servs.*, 66 F. Supp. 3d 217 (D.D.C. 2014). FDA previously approved Neurontin, a gabapentin drug first developed by Pfizer. *Id.* at 223. Pfizer, however, had not sought orphan drug designation or exclusivity for Neurontin. *Id.* at 223-24. FDA eventually granted an amended request for orphan drug designation for Gralise, finding that the data presented was adequate to show a plausible hypothesis of clinical superiority over Pfizer’s

Neurontin. *Id.* at 225-26. However, when FDA approved Gralise, the agency determined that the sponsor had not demonstrated that Gralise was in fact clinically superior to Neurontin—meaning that it was the same drug as Neurontin and, therefore, not eligible for orphan drug exclusivity. *Id.* at 226.

Depomed argued that it was not required to demonstrate clinical superiority because exclusivity should have been automatic once FDA designated and approved Gralise. *Id.* at 220. The district court agreed, and ordered FDA to recognize exclusivity for Gralise, noting that the case did “not raise the specter of the ‘serial exclusivity’ scenario,” because the first approved drug, Neurontin, had not itself received a period of orphan drug exclusivity. *Id.* at 237. The district court concluded that the facts in *Depomed* were *sui generis* because serial exclusivity “rarely, if ever, actually occurs.” *Id.* at 236-37.

FDA complied with the district court order for *Depomed*, but subsequently published a notice in the Federal Register announcing that the agency would continue to implement its long-standing clinical superiority framework for designation and exclusivity decisions. *See* Policy on Orphan-Drug Exclusivity: Clarification, 79 Fed. Reg. 76,888 (Dec. 23, 2014) [FDA 1839].⁸

D. FDA Reauthorization Act of 2017

The version of the statute analyzed by the Court in *Depomed* remained in effect until earlier this year, when the President signed into law the FDA Reauthorization Act of 2017 (FDARA). *See* FDARA, Pub. L. No. 115-52, 131 Stat. 1005 [FDA 1840-1925]. Among other things, the FDARA amended the Orphan Drug Act, explicitly incorporating FDA’s existing

⁸ FDA explained that it would continue to interpret 21 U.S.C. § 360cc and regulations—both the 1992 regulations, which apply here, and those promulgated in 2013, *see supra* note 6—“to require the sponsor of a designated drug that is the ‘same’ as a previously approved drug to demonstrate that its drug is ‘clinically superior’ to that drug upon approval in order for the subsequently approved drug to be eligible for orphan-drug exclusivity.” 79 Fed. Reg. 76,888 [FDA 1839].

approach to orphan drug exclusivity into the language of the statute. Specifically, the statute provides:

If a sponsor of a drug that is designated under section 526 and is otherwise the same, as determined by the Secretary, as an already approved . . . drug is seeking exclusive approval . . . for the same rare disease or condition as the already approved drug, the Secretary shall require such sponsor, as a condition of such exclusive approval . . . to demonstrate that such drug is clinically superior to any already approved . . . drug that is the same drug.

Id. § 607(a)(3) [FDA 1884]. Further, the FDARA includes a “Rule of Construction,” which expressly preserves FDA’s pre-enactment exclusivity determinations: “Nothing in the amendments shall affect any determinations under [the exclusivity provision of the Orphan Drug Act] made prior to the date of enactment.” *Id.* § 607(b) [FDA 1885].

II. STATEMENT OF FACTS

UTC developed the drug at issue in this case, Orenitram, for the treatment of pulmonary arterial hypertension (PAH). PAH is a disease characterized by restricted blood flow in the pulmonary arterial circulation, which can result in increased pulmonary vascular resistance and right heart failure.⁹ Orenitram contains the active ingredient treprosintil, and delivers it in the form of an extended-release oral tablet. Orenitram is the third treprosintil drug that UTC has developed to treat PAH.

A. UTC Obtains Orphan Drug Exclusivity For Remodulin (Intravenous And Subcutaneous Treprostnil)

UTC developed the first such drug, Remodulin (intravenous and subcutaneous treprostnil), sometime before 2000. In 1999, FDA granted UTC’s request to designate Remodulin as an orphan drug for the treatment of PAH. *See* Letter from Dean Bunce, United

⁹ *See* Vallerie V. McLaughlin et al., *ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension*, 119 *Circulation* 2250, 2252-53 (2009) [FDA 643-44].

Therapeutics Corp., to Marlene Haffner, FDA (Oct. 13, 1999) [FDA 1416-1653]; Letter from Marlene E. Haffner, FDA, to Dean Bunce, United Therapeutics Corp. (Nov. 2, 1999) [FDA 1668]. Subsequently, FDA approved Remodulin for the treatment of PAH in subcutaneous and intravenous uses. *See* Letter from Robert Temple, FDA, to Dean Bunce, United Therapeutics Corp. (May 21, 2002) [FDA 1670-73]; Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (Nov. 24, 2004), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021272 Orig1s002.pdf.

On June 5, 2002, FDA recognized seven-year orphan drug exclusivity for Remodulin as the first sponsor of treprostinil to obtain marketing approval for PAH, with the exclusivity period expiring on May 21, 2009. *See* Letter from Marlene E. Haffner, FDA, to Dean Bunce, United Therapeutics Corp. (June 5, 2002) [FDA 1687-89].

B. UTC Obtains Orphan Drug Exclusivity For Tyvaso (Inhaled Treprostinil) On The Basis Of Clinical Superiority

After Remodulin, UTC developed and sought orphan drug designation for Tyvaso, an inhaled formulation of treprostinil, for the treatment of PAH.¹⁰ *See* Letter from Mary L. Grice,

¹⁰ Designation is “conferred to the active moiety rather than the product formulation” and “changes to the product formulation should not generally affect orphan drug designation status.” *See* FDA, *For Industry, Developing Products for Rare Diseases & Conditions, Designating an Orphan Product: Drug and Biological Products, Frequently Asked Questions (FAQ)*, <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm240819.htm> (last visited Dec. 6, 2017) (hereinafter “Orphan Drug Designation FAQ”); *see also* Letter from Gayatri R. Rao, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., at 1–2 (Mar. 23, 2016) [FDA 443-33]. For purposes of exclusivity, however, the changed formulation will not receive a new period of exclusivity “unless the sponsor can demonstrate that the changed formulation is clinically superior to the original approved product.” *See* Orphan Drug Designation FAQ. Accordingly, because FDA previously granted orphan drug designation to UTC for treprostinil in the treatment of PAH (*i.e.*, for Remodulin), UTC was not technically required to submit a request to designate Tyvaso for the treatment of PAH. In order for FDA to recognize exclusivity for Tyvaso, UTC was required to demonstrate that Tyvaso is clinically superior to Remodulin.

FDA, to Robert Roscigno, Lung Rx, Inc. (May 11, 2004) [FDA 779].¹¹ In the request, UTC argued that Tyvaso was clinically superior because it showed “greater safety” as compared to Remodulin by “eliminat[ing] the most common treatment-related adverse events experienced by patients [i.e., infusion site pain and reaction].” *See* FDA Review of Request for Orphan-Drug Designation: Designation Request 04-1891, at 4 [FDA 784] (internal quotations omitted). UTC also argued that the “change in treprostinil dosage forms from subcutaneous to inhalation is a type of change FDA has recognized as a viable candidate for demonstrating clinical superiority based on a major contribution to patient care.” *Id.* (internal quotations omitted).

FDA concluded that UTC had not presented a plausible hypothesis of clinical superiority, because a “convincing hypothesis of greater safety cannot be meaningfully entertained until at least some clinically-relevant evidence of comparable treatment effectiveness has been established.” *See* Letter from Marlene E. Haffner, FDA, to Frank Sasinowski, Hyman, Phelps & McNamara, P.C., at 2 (Sept. 22, 2004) [FDA 790]. Absent any clinical data on Tyvaso, it was unclear whether Tyvaso, as compared with Remodulin, was associated with similarly frequent and serious adverse events.

On March 16, 2009, UTC submitted an amended designation request. *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Timothy Coté, FDA (Mar. 16, 2009) [FDA 801-967]. In anticipation of a meeting with FDA to discuss its designation request, UTC also submitted additional materials on July 20, 2009. *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Timothy Coté, FDA (July 20, 2009) [FDA 990-1111]. On August 4, 2009, UTC submitted a second amended designation request. *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Timothy Coté, FDA (Aug. 4, 2009)

¹¹ United Therapeutics Corp. was previously known as Lung Rx, Inc. *See* Letter from Dean Bunce, United Therapeutics Corp., to Marlene Haffner, FDA (Oct. 15, 1999) [FDA 1665].

[FDA 1132-1186]. In these supplemental materials, UTC included additional data on adverse events associated with Tyvaso and Remodulin.

On July 30, 2009, FDA approved Tyvaso for the treatment of PAH. *See* Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (July 30, 2009) [FDA 1112-17]. On April 6, 2010, at UTC's request, the company again met with FDA to discuss designating Tyvaso as an orphan drug. *See* Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (May 3, 2010) [FDA 1197-1201].

After meeting with the company and reviewing the additional materials submitted to support a claim of clinical superiority, FDA found that UTC had demonstrated clinical superiority of Tyvaso over Remodulin. Although both drugs were associated with different adverse events, in light of the data related to severe injection-site pain for Remodulin patients, FDA concluded that Tyvaso "offered a valuable alternative for someone who found the pain caused by subcutaneous infusion intolerable or who found a central venous line burdensome." *See* FDA Mem. of Meeting Minutes, at 3 (Apr. 6, 2010) [FDA 1199]. Accordingly, on June 17, 2010, FDA granted orphan drug designation and recognized orphan drug exclusivity for Tyvaso in the treatment of PAH. *See* Letters from Timothy R. Coté, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C. (June 17, 2010) [FDA 1214-18]. UTC's second period of exclusivity expired on July 30, 2016.

C. UTC Fails To Establish That Orenitram (Oral Treprostinil) Is Entitled To Orphan Drug Exclusivity

Before the expiration of UTC's orphan drug exclusivity for Tyvaso, the company began development of the drug at issue here, Orenitram, treprostinil in an extended-release oral tablet. On December 14, 2011, UTC requested orphan drug designation for Orenitram in the treatment of PAH. *See* Letter from Dean Bunce, United Therapeutics Corp., to Gayatri Rao, FDA (Dec.

14, 2011) [FDA 1-351]. In its request, UTC argued there was a plausible hypothesis of clinical superiority because Orenitram presented a major contribution to patient care in that the drug did not present the same limitations associated with an infusion pump (for subcutaneous and intravenous use) or a nebulizer (for inhaled use). *Id.* at 17-18 [FDA 18-19]. Instead, UTC argued, Orenitram was an oral tablet that is “simple, patient-friendly, and convenient.” *Id.* at 18 [FDA 19]. On March 9, 2012, FDA issued a deficiency letter in response to UTC’s orphan drug designation request for Orenitram. *See* Letter from Gayatri R. Rao, FDA, to Rex Mauthe, United Therapeutics Corp. (Mar. 9, 2012) [FDA 366-69].

On December 20, 2013, FDA approved Orenitram for the treatment of PAH. *See* Letter from Norman Stockbridge, FDA, to Dean Bunce, United Therapeutics Corp. (Dec. 20, 2013) [FDA 370-73]. Two years later (and four years after its original application), on December 7, 2015, UTC amended its designation request, offering three hypotheses for clinical superiority: “(A) that oral treprostinil has greater long-term efficacy than inhaled treprostinil; (B) that oral treprostinil’s dosing flexibility provides greater safety in the target population versus Tyvaso; and (C) that oral treprostinil provides a MCTPC [major contribution to patient care] over Tyvaso because of the differential impact on patients’ daily lives.” *See* Letter from Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., to Gayatri R. Rao, FDA, at 6 (Dec. 7, 2015) [FDA 399].

On March 23, 2016, FDA responded to UTC’s amended request and explained that because orphan drug designation typically covers the active moiety, not the formulation, Orenitram was covered under UTC’s previous orphan drug designation for the active moiety treprostinil for use in the treatment of PAH.¹² *See* Letter from Gayatri R. Rao, FDA, to Frank J. Sasinowski, Hyman, Phelps & McNamara, P.C., at 1 (Mar. 23, 2016) [FDA 443-33]. FDA then

¹² *See supra* note 10.

carefully evaluated UTC's arguments in support of clinical superiority, and found them to be insufficient.¹³ Among other things, the agency noted that because the adverse events listed in Orenitram's labeling appeared to be similar to those described in the Tyvaso labeling, UTC had not demonstrated greater safety over Tyvaso. *Id.* at 2 [FDA 444]. Nor had UTC addressed the complexities and inconveniences of administering drugs orally. For example, because Orenitram must be taken with food, a patient taking Orenitram must schedule his daily activities around when he has access to food with sufficient caloric and fat content. *Id.* at 2-3 [FDA 444-45]. The dosing schedule for Orenitram is also complex, such that some patients—particularly those who are mentally challenged or elderly—may have difficulty adhering to the schedule. *Id.* at 3 [FDA 445]. Accordingly, FDA found that UTC failed to demonstrate that Orenitram was entitled to orphan drug exclusivity. *See id.* [FDA 445].

D. Current Litigation

On August 4, 2017, UTC filed a complaint for declaratory and injunctive relief against the United States. The Complaint alleges that FDA “impermissibly denied Orenitram orphan drug exclusivity and required that UTC demonstrate that Orenitram is clinically superior to Remodulin and Tyvaso.” Compl. ¶ 37. UTC thus alleges that “Defendants’ denial of orphan drug exclusivity . . . was arbitrary and capricious, an abuse of discretion, exceeds Defendants’ statutory authority, and is otherwise not in accordance with the law.” *Id.*

¹³ FDA's March 23, 2016 letter only addressed arguments UTC raised before the agency. Neither UTC's original application, nor its supplemental materials, presented FDA with the legal arguments it now raises in this lawsuit—namely, that Orenitram is automatically entitled to an additional exclusivity period upon approval and designation, and that the clinical superiority framework exceeds FDA's statutory authority. To the contrary, UTC acknowledged and accepted the applicability of the clinical superiority framework, and the company offered several hypotheses of clinical superiority.

Exhibit 1 redacted for brevity
(Pages 15 – 29 deleted)

CONCLUSION

For these reasons, we respectfully request that the Court deny UTC's motion for summary judgment, and enter summary judgment in favor of the United States.

Respectfully submitted,

CHAD A. READLER
Acting Assistant Attorney General

ETHAN DAVIS
Deputy Assistant Attorney General

GUSTAV W. EYLER
Acting Director

ANDREW E. CLARK
Assistant Director

s/ Alexander V. Sverdlov
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December 22, 2017

Attorneys for Defendants

EXHIBIT 2

Office of Orphan Products Development(HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 15, 1994

Reckitt & Colman Pharmaceuticals, Inc.
Attention: Mr. Charles O'Keeffe
Executive Vice President
1901 Huguenot Road
Richmond, VA 23235

Dear Mr. O'Keeffe:

Reference is made to your orphan drug application of May 5, 1993 submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (FFDCA) for the designation of buprenorphine hydrochloride as an orphan drug (application [REDACTED]). We also refer to your amendment dated November 15, 1993.

We have completed the review of this application, as amended, and have determined that buprenorphine qualifies for orphan designation for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B) of the FFDCA. Please note that it is buprenorphine and not its formulation that has received orphan designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if buprenorphine were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

In addition, please inform this office annually as to the status of the development program, and at such time as a marketing application is submitted to the FDA for the use of buprenorphine as designated. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. John McCormick at (301) 443-4718.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director

cc:

GCF-1/J.Cohen

HFD-85/M.A.Holovac

HFD-007

HF-35/OP File [REDACTED]

HF-35/B.Steeves

HF-35/chron

HF-35/P.Vaccari 6/15/94 dsg.752

2 6/15/94

EXHIBIT 3

FILE COPY

Review of a Request for Orphan Drug Designation

Date of submission: May 5, 1993
Received by reviewer: May 6, 1993
Review initiated: June 1, 1993
Review completed: June 25, 1993

Designation [REDACTED]

Drug Name:

code name:

generic name: buprenorphine hydrochloride

trade name: not yet assigned

Sponsor's Name:

Reckitt & Colman Pharmaceuticals, Inc.
1901 Huguenot Road
Richmond, Virginia 23235

Contact Person:

Charles O'Keeffe
Executive Vice President
Reckitt & Colman Pharmaceuticals, Inc.
1901 Huguenot Road
Richmond, Virginia 23235
(804) 379-1090

Drug Manufacturer:

Active drug substance and finished dosage form is manufactured by:

[REDACTED]

[REDACTED]

Proposed Designation:

For use in treatment-seeking opiate users in opiate detoxification and maintenance treatment schedules.

Regulatory Status:

Buprenorphine is presently marketed in the United States as an injectable analgesic under NDA 18-401. The sublingual formulation has not been approved; however, it is being studied under 4 IND's in the U.S.. Both the injectable and the sublingual are marketed in numerous countries outside of the U.S. as an analgesic.

Disease/Condition Background Information:

The primary characteristic of opiates which promotes abuse is the feeling of euphoria, described as a high. The euphoria in addition to the analgesic effect also makes the opiates a very effective treatment for disease initiated pain. Most opioid abuse begins when users are in their teens, and if use continues, addiction develops in one to two years. Chronic use is accompanied by delayed or arrested development in most areas of an addicts life, including their educational, occupational, and psychosexual lives. Chronic use also results in tolerance and the addict needs ever increasing doses to achieve a high. With the development of tolerance the addict also develops physical dependence which results in a withdrawal syndrome 8 to 10 hours after the last injection. Withdrawal, in most instances, is comparable to a severe case of the flu and is not life threatening; however, prevention of withdrawal syndrome seems to be a significant motivator in the addicts search for drug. In addition to withdrawal, other side effects of opiate addiction include criminal behavior to secure the money necessary to purchase drug, and acute heroin reaction, which is usually caused by the ingredients used to cut street heroin. Treatment consists of two phases, the first involves reducing or eliminating withdrawal syndrome, and the second is to eliminate drug seeking behavior. Medically assisted withdrawal is usually accomplished by treating the withdrawing addict with methadone which is gradually tapered over seven days. An alternative therapy is treatment with clonidine when methadone is not available. Multiple therapies have been tried to eliminate the drug seeking behavior and include maintenance of addicts on methadone, psychoanalysis, group therapy, and opioid antagonists.

Population Estimate:

The sponsor states that there are approximately 115,000 patients enrolled in methadone maintenance programs in the United States, and 3,000 patients being treated with naltrexone. They then imply that this represents most "treatment seeking" patients in the country; however, they do mention other types of treatment programs, without giving enrolment estimates for these programs.

Rationale for Use:

Buprenorphine appears to be a very long acting semi-synthetic opioid with both agonist and antagonist properties. When given to patients experiencing withdrawal, it will mitigate and delay the onset of symptoms. It has also be reported to be effective as a maintenance agent, with less physical dependency than methadone. The sponsor implies that it will be an effective agent to transfer patients from methadone maintenance to agonist therapy.

Evaluation and Recommendation:

There is adequate clinical evidence to support the designation of buprenorphine, the problem with this application is the size of the intended population. Most sources estimate the number of opioid addicts at 1,000,000 to 1,500,000. The sponsor states that approximately 120,000 of these addicts are presently on drug therapy, and this represents the size of the population likely to use a pharmacologic agent. Without specifying some characteristic of the drug which would limit its use, it is difficult for this office to accept such a limitation on a population. The law specifically uses the words disease or condition, and does not mention those who are likely to use the product or seek treatment; therefore, it would seem reasonable to assume that if there are 1,000,000 opioid addicts then the disease or condition which this drug is intended to treat contains a population of 1,000,000 patients. It should also be noted that for opioid addiction the number of addicts seeking treatment varies according to a number of factors such as the price of heroin, and the addicts access to funds to pay for illicit drugs; therefore, the number of patients seeking treatment may represent a very variable number. In addition, the present application does not specify how many patients are in treatment, since the sponsor makes no attempt to provide a number for the patients which are treated in programs that are not a part of the methadone clinics.

The sponsor should be informed that:

It is unclear from your application how many addicts are "treatment-seeking" since you do not provide the number of patients in treatment programs other than methadone maintenance clinics. It is also unclear why "treatment-seeking" should be considered a medically plausible subset as defined by the recently published regulations, since there does not seem to be any characteristic of the drug which would preclude its use in any opiate addicted patient.

As an alternative to justifying a designation by limiting the number of addicts available for treatment, you may wish to consider requesting designation because it is unlikely that the sales of buprenorphine in the United States will be adequate to recover the preclinical and clinical development cost within 7 years of approval. As you may be aware congress provided for drugs which may be "orphans" for reasons other than the size of the population they are intended to treat, by allowing this office to designate drugs based on their expected lack of profitability. This approach has not been used since the amendments to the Orphan Drug Act were passed in 1985; however, it would seem that this product may be designatable under this portion of the statute. We are enclosing a copy of the pertinent regulations, and should you have any questions relating to the process of applying for designation because of an expected lack of profitability, you may wish to contact Mr. Robert Steeves J.D. of this office.

John J. McCormick

John J. McCormick, M.D.

Medical Reviewer, Office of
Orphan Products Development
(HF-35)

Concur: *Marlene E. Haffner* Date: *6/28/93*

Marlene E. Haffner, M.D.

cc:

HF-35/Designation File 

HF-35/Chron File

HF-35/Jmccormick

c:buprenor.752

EXHIBIT 4

Review of a Request for Orphan Drug Designation

FILE COPY

Date of submission: May 5, 1993
Received by reviewer: May 6, 1993
Review initiated: June 1, 1993
Review completed: June 25, 1993
Date Supplement Received: November 17, 1993
Date Further Supplement Received: February 7, 1994
Date Review Completed: June 14, 1994

Designation: [REDACTED]

Drug Name:

code name:

generic name: buprenorphine hydrochloride

trade name: not yet assigned

Sponsor's Name:

Reckitt & Colman Pharmaceuticals, Inc.

1901 Huguenot Road

Richmond, Virginia 23235

Contact Person:

Charles O'Keeffe

Executive Vice President

Reckitt & Colman Pharmaceuticals, Inc.

1901 Huguenot Road

Richmond, Virginia 23235

(804) 379-1090

Drug Manufacturer:

Active drug substance and finished dosage form is manufactured by:

[REDACTED]
[REDACTED]

Proposed Designation:

For use in treatment-seeking opiate users in opiate detoxification and maintenance treatment schedules.

Regulatory Status:

Buprenorphine is presently marketed in the United States as an injectable analgesic under NDA 18-401. The sublingual formulation has not been approved; however, it is being studied

under 4 IND's in the U.S.. Both the injectable and the sublingual are marketed in numerous countries outside of the U.S. as an analgesic.

Evaluation and Recommendation:

Prior review of the sponsor's application found that there is adequate clinical evidence to support the designation of buprenorphine, but identified a substantial concern with this application because of the size of the intended population. Most sources estimate the number of opioid addicts at 1,000,000 to 1,500,000. The sponsor stated that approximately 120,000 of these addicts are presently on drug therapy, and this represented the size of the population likely to use a pharmacologic agent. Without specific characteristics of the drug which would limit its use, OPD would not accept such a limitation on a population and concluded that it was reasonable to assume that if there are 1,000,000 opioid addicts then this is also the prevalence of the disease or condition which this drug is intended to treat. It should also be noted that for opioid addiction the number of addicts seeking treatment varies according to a number of factors such as the price of heroin, and the addicts access to funds to pay for illicit drugs; therefore, the number of patients seeking treatment may represent a very fluctuating number.

In addition, the prior application did not specify how many patients are in treatment, since the sponsor makes no attempt to provide a number for the patients which are treated in programs that are not a part of the methadone clinics.

The sponsor received an incomplete letter stating these deficiencies and was informed that:

It is unclear from your application how many addicts are "treatment-seeking" since you do not provide the number of patients in treatment programs other than methadone maintenance clinics. It is also unclear why "treatment-seeking" should be considered a medically plausible subset as defined by the recently published regulations, since there does not seem to be any characteristic of the drug which would preclude its use in any opiate addicted patient.

As an alternative to justifying a designation by limiting the number of addicts available for treatment, you may wish to consider requesting designation because it is unlikely that the sales of buprenorphine in the United States will be adequate to recover the preclinical and clinical development cost within 7 years of approval. As you may be aware congress provided for drugs which may be "orphans" for reasons other than the size of the population they are intended to treat, by allowing this office to designate drugs based on their expected lack of profitability. This approach has not been used since the amendments to the Orphan Drug Act were passed in 1985; however, it would seem that this product may be designatable under this portion of the statute. We are enclosing a copy of the pertinent regulations, and should you have any questions relating to the process of applying for designation because of an expected lack of profitability, you may wish to contact Mr. Robert Steeves J.D. of this office.

The sponsor has responded to these deficiencies and issues by providing additional information.

REVIEW OF SUPPLEMENTARY MATERIALS AND RECOMMENDATIONS:

Prior review of the sponsor's application resulted in a determination that the patient prevalence for opiate addiction easily exceeded the 200,000 patient figure established by law as the upper limit for orphan designation. The Office indicated its intention to reject the argument that since the number of treatment slots available under state and federal antiaddiction programs has been steady at 104,000, that that figure should be assumed to be the potential treatable addict population. A series of meetings with the sponsor, and representative of the National Institutes on Drug Abuse ensued over several months because NIDA wished to have a Cooperative Research and Development Agreement with the sponsor for the development of this addiction treatment, and the sponsor was unwilling to proceed without the exclusivity that orphan designation would provide under the circumstances.

Without relinquishing the right to pursue or challenge the population/prevalence arguments, the sponsor submitted a supplemental request for designation under Section 526(a)(2)(B) on the basis that "there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."

The sponsor submitted a financial spreadsheet showing its projected cumulative costs and returns for the years 1993 thru 2002 which included the assumption that the product would be first marketed in 1995. The financial submission was accompanied by "a report of an independent certified public accountant in accordance with [the] Statement on Standards for Attestation established by the American Institute of Certified Public Accountants on agreed upon procedures performed with respect to data estimates and justifications submitted" The reviewer consulted with AICPA on the nature and content of the report anticipated by its Statement and concluded that the [redacted] letter and attachments dated 11 November 1993 meets the requirement set forth in the orphan drug regulations, 21 CFR s 316.21(b)(8). Since the certificate necessarily relates to projections of costs and allocations, it is not an audit of completed transactions and thus appropriately carries a caution that "actual results may vary considerably from those shown."

The sponsor also submitted with its supplemental request excerpts from the CRADA with NIDA for the development of this drug which showed that in addition to the [redacted] future costs the sponsor was agreeing to expend on behalf of the CRADA, it had or would incur another [redacted] in expenses related to the development of buprenorphine. However, the sponsor declined to provide more precise expenditure expense estimates or records because it felt that the cost of collecting and evaluating the allocations for these records retrospectively over a period of years would not be cost effective; furthermore, the sponsor believed that the CRADA expenses alone would meet the requirements for designation.

Included within the listing was an item identified as "Preclinical Reckitt & Colman expenditures" for [REDACTED]. Because the reviewer was aware of the close involvement of NIDA on the figures submitted as part of the CRADA, and the potential costs of the project, the reviewer requested NIDA estimate the cost and value of the buprenorphine preclinical studies (to independently verify the figures submitted by the sponsor). In a letter dated April 13, 1994, NIDA responded that "based on the list of preclinical studies supplied to NIDA and in consultation with scientists and administrators here, I would conservatively estimate the current value of the data base . . . to be in the range of [REDACTED]. NIDA noted that it was of some importance to them that this data would require 3 to 5 years to obtain or recreate outside of the CRADA. This reviewer is satisfied that financial estimates and projections, including those fully incorporated in the request for designation, are fair and reasonable estimates.

To assess the likelihood that this request meets the statutory requirement that "there is no reasonable expectation" that sales over the first 7-year period will permit recovery of the developmental costs, the sponsor's spreadsheet was reconstructed (Lots 1-3) and subjected to additional hypotheses that might affect the first 7 years of marketing results. Where delays are included in the calculations, the year-dates remain unchanged in the charts. The delay period appears as "XX" or some variation in order to keep the marketing period results clear and comparable. Obviously, if the NDA is first approved in 1998, then the exclusivity period relevant for the statutory assessment begins in 1998 and ends 7 years later.

Chart 1 is a simple reconstruction of the sponsor's spreadsheet which establishes the validity of the formulas and interrelationships of prevalence, sales, cost recovery, etc. It demonstrates that if the product were approved and marketed in 1995, the excess of development costs in 2001 (7 years later) would be [REDACTED] (last column of line 19, Chart 1).

Chart 2 is the same data as used above, but adds an assumption that marketing approval is not forthcoming until two years later than shown in Chart 1. Since the IND's had just been submitted in May, 1994, the CRADA has just been formally agreed to with NIDA, and 1994 is half over, it seems reasonable to conclude that marketing approval is at least two or more years away. Chart 2 projects that the unrecovered costs 7 years after marketing would be a [REDACTED]

Chart 2A is a variation on the above two with the added assumption that the delay in marketing approval will be at least three years in the future. The projection here is that the first 7 years of marketing experience will produce [REDACTED]

Charts 3A and 3B test the effects of assuming the sponsor estimates of the patient population market obtained should be fifty percent higher in all phases of the project. Chart 3A used the 1995 marketing date assumption, Chart 3B assumes a two-year delay. These charts can also be considered surrogates for an assumption that the 104,000 patient treatment group should be increase by fifty percent (up to 156,000) but that the market share for buprenorphine (in %)

remains as estimated by the sponsor. Chart 3A shows [REDACTED] whereas Chart 3B shows [REDACTED]

Charts 4 and 4A are similar to Charts 3A & 3B, except that the patient market is doubled (a 100% increase over the sponsor estimates). Chart 4 shows [REDACTED] and Chart 4A project [REDACTED] with a 2-year delay in NDA approval).

Charts 6 and 6A address price. The assumption in all prior calculations is that at the [REDACTED] per dose charge cannot be increased because of the unique characteristics of the market. However, these charts are a "what if" the price could be increased by [REDACTED]. In this case, ---and the patient estimates were doubled. Under these circumstances, Chart 6 shows a [REDACTED] and Chart 6A (with a 2-year delay) show [REDACTED]

The sponsor maintains that the price competition between its product and methadone will effectively curtail any increases in price. The sponsor projects an annual patient cost of [REDACTED] per year (which is the figure used in all the above charts and analyses), and compares that with [REDACTED] for LAAM and [REDACTED] for methadone. Their theory is that since most of these products are purchased by treatment centers, governments, etc., rather than individuals, it is unlikely that buprenorphine will supplant any of the market for the cheaper products. This seems to be a reasonable conclusion. The sponsor also notes that the cost of manufacturing buprenorphine is much greater than for methadone, so that (a) buprenorphine profits will be slimmer and (b) methadone is and remain more cost competitive in the future. The sponsor notes that while the pricing has not been established for the product, they have already concluded that the competitive agents will not permit the usual and full markup it would ordinarily consider for a new indication. This obviously will limit further their ability to recoup the development costs.

Additionally, the sponsor states that any increase in the price charged would decrease the market penetration, so that an increase in price would not proportionally or necessarily increase total sales, or profits. This states the obvious, but unlike the lethargic relationship expected for increases in sales or market shares, the negative effect on market share reduction in the circumstances of drug treatment centers is likely to be much more dramatic and immediate.

The sponsor maintains that the maximum number of treatment-seeking addicts that could be treated is limited to 104,000 since there are only 115,000 treatment slots for methadon, et al., in existing drug treatment facilities. This argument was considered and rejected as a rationale for designating this product on the basis of a prevalence of 200,000 or less; however, it is relevant in estimating the marketing potential for the product. It is not reasonable to posit that the drug-abusing population will en masse switch to this product. It is reasonable to assume that there will be virtually no change in the treatment-seeking population, or that any positive shift will be incremental. Thus, over seven years, the additional patients on this product beyond those projected by the sponsor should be inconsequential economically on the results of this analysis.

those projected by the sponsor should be inconsequential economically on the results of this analysis.

This reviewer concludes that the patient population estimates and market shares submitted by the sponsor are reasonable and fair, and that projections verify that the statutory requirement that there is no reasonable expectation that the development costs will be recovered in the first 7 years of marketing has been satisfied.

The data from the charts are shown in graph form, per the attached.

It is recommended that buprenorphine hydrochloride be designated an orphan product for the treatment of opiate addiction in opiate users under Section 526(a)(2)(B).

Robert E. Steeves, R.Ph., LL.M.
Office of Orphan Products Development

Concur:

Date:

Marlene E. Haffner, M.D., M.P.H.

cc:

HF-35/Designation File
HF-35/Chron File
HF-35/Jmccormick
c:\wp51\desigs\bupreno2.rpt

EXHIBIT 5



[FDA Home](#)³ [Developing Products for Rare Diseases & Conditions](#)⁴

Search Orphan Drug Designations and Approvals

Generic Name: Buprenorphine hydrochloride
Trade Name: Subutex; Sublocade
Date Designated: 06/15/1994
Orphan Designation: Treatment of opiate addiction in opiate users.
Orphan Designation Status: Designated/Approved
Marketing Approval Date: 11/30/2017
Approved Labeled Indication: SUBLOCADE is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
Exclusivity End Date: TBD
Sponsor: Indivior, Inc.
 10710 Midlothian Turnpike
 Suite 430
 Richmond, Virginia 23235
 USA

The sponsor address listed is the last reported by the sponsor to OOPD.

Generic Name: Buprenorphine hydrochloride
Trade Name: Subutex; Sublocade
Date Designated: 06/15/1994
Orphan Designation: Treatment of opiate addiction in opiate users.
Orphan Designation Status: Designated/Approved
Marketing Approval Date: 10/08/2002
Approved Labeled Indication: Treatment of opioid dependence in patients 16 years of age or older
Exclusivity End Date: 10/08/2009
Sponsor: Indivior, Inc.
 10710 Midlothian Turnpike
 Suite 430
 Richmond, Virginia 23235
 USA

The sponsor address listed is the last reported by the sponsor to OOPD.

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EXHIBIT 6

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Alcohol and Opioid Dependence Medications: Prescription Trends, Overall and by Physician Specialty

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Abstract

Over the past decade, advances in addiction neurobiology have led to the approval of new medications to treat alcohol and opioid dependence. This study examined data from the IMS National Prescription Audit (NPA) PlusTM database of retail pharmacy transactions to evaluate trends in U.S. retail sales and prescriptions of FDA-approved medications to treat substance use disorders. Data reveal that prescriptions for alcoholism medications grew from 393,000 in 2003 (\$30 million in sales) to an estimated 720,000 (\$78 million in sales) in 2007. The growth was largely driven by the introduction of acamprosate in 2005, which soon became the market leader (\$35 million in sales). Prescriptions for the two buprenorphine formulations increased from 48,000 prescriptions (\$5 million in sales) in the year of their introduction (2003) to 1.9 million prescriptions (\$327 million in sales) in 2007. While acamprosate and buprenorphine grew rapidly after market entry, overall substance abuse retail medication sales remain small relative to the size of the population that could benefit from treatment and relative to sales for other medications, such as antidepressants. The extent to which substance dependence medications will be adopted by physicians and patients, and marketed by industry, remains uncertain.

Keywords

alcoholism; opioid dependence; acamprosate; buprenorphine; disulfiram; naltrexone

1. Introduction

Few medications exist to treat substance dependence. Until 1994, only disulfiram was approved by the Food and Drug Administration (FDA) to treat alcoholism. Pharmacotherapies for opioid dependence consisted solely of methadone maintenance and naltrexone treatment. Methadone is strictly regulated federally and is not available through retail pharmacies and naltrexone has not been widely prescribed for this indication. Over the past decade, however, advances in addiction neurobiology have led to the approval of two new medications to treat alcohol dependence and one medication to treat opioid dependence (available through prescription by community physicians with appropriate federal approval). This study aimed to gain a broader understanding of the market diffusion of these medications in the United States. Although the results are not generalizable internationally,

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because the availability and use of medications to treat alcoholism and opioid dependence differs across countries, the findings may have implications for industry investment in substance abuse medications which may ultimately influence their availability in a variety of countries.

Trends in U.S. sales volume, number of prescriptions, and prices for retail medications that are FDA-approved for the treatment of alcohol dependence (i.e., disulfiram, naltrexone and acamprosate), and opioid dependence (i.e., buprenorphine) are presented. Because previous studies have shown that physician specialty is associated with early adoption of new alcoholism medications, market size potential, the receipt of ancillary psychotherapeutic services, and the level of adherence (Mark et al., 2003, Powers et al., 2002, Robinson et al., 2006), we also examined prescription volume by medical specialty of the provider.

2. Methods

This study is based on data from the IMS National Prescription Audit (NPA) PlusTM database of retail pharmacy transactions for the period of 2002 through August 2007. NPA Plus provides information on the volume of new and refilled prescriptions categorized by the specialty of the prescribing physician. The NPA Plus consists of transaction records from retail pharmacies, including those at chain, independent, food store and mass merchandiser pharmacy retail outlets. When weighted, these sources represent all prescriptions filled in retail outlets in the United States. The database does not include mail order transactions; transactions at pharmacies in HMOs serving members only; or dispensing at hospitals or clinics or directly to patients by physicians or home health agencies.

IMS collects NPA Plus information each month from a sample panel of 20,000–36,000 retail pharmacies, representing about 40% of all such pharmacies (IMS National Prescription Audit PlusTM, 2005). IMS assigns physician specialty information based primarily on each physician's Drug Enforcement Administration number, which is included in a separate, larger sample of retail pharmacy transactions.

The study examined retail prescriptions of medications with FDA-approved indications for the treatment of alcohol or opioid dependence. Generic and name brand prescriptions for the following medications were examined: ReVia®/naltrexone, Vivitrol®/naltrexone IM, Antabuse®/disulfiram, Campral®/acamprosate, Subutex®/buprenorphine hydrochloride, and Suboxone®/buprenorphine hydrochloride/naloxone. For comparison purposes, data were also obtained from IMS on the number of prescriptions and sales for all antidepressants, and for one recently-marketed antidepressant, Lexapro®. Data on total dollar sales, number of prescriptions, price per prescription, and prescriptions by provider specialty were also obtained. The drivers of sales volume can be decomposed using figures for prescription volume and price. Information for the period January through August of 2007 was annualized by multiplying the data by 12/8.

3. Results

All substance dependence medications

In 2007, the number of prescriptions for alcohol and opioid dependence medications totaled 2.6 million, more than a six-fold increase from 2002 (Table 1). In 2007, nearly three times as many prescriptions were filled for opioid medications as for alcoholism medications (1,910,000 vs. 705,000, respectively). From 2003 to 2007, total dollar sales volume for retail substance dependence medications grew at a 62.2% average annual growth rate (from \$32 million to \$406 million) (Table 1). Although growth over the six-year period was strong, the market for alcoholism and opioid dependence medications remained small relative to the

antidepressant market. In 2006 more than 226 million antidepressant prescriptions were filled, equaling \$15 billion in sales.

Alcoholism treatment medications

Prescriptions for alcoholism treatment medications increased at a 12.9% average annual growth rate (from 393,000 in 2003 to an estimated 720,000 in 2007) (Table 1). The growth was largely driven by the addition of acamprosate to the alcoholism market, which occurred in 2005. Just two years after its introduction, the number of acamprosate prescriptions had grown to 293 million in 2006, surpassing those for naltrexone (Table 1). The number of prescriptions for disulfiram decreased steadily from 2003 through 2007 at an annual average rate of -3.0%. By 2007, long-acting injectable naltrexone, introduced in 2006, had captured only a small portion of the market.

As of 2007, acamprosate had the highest sales volume among alcoholism medications, reaching an estimated \$35 million, followed by oral naltrexone at \$22 million. Sales of long-acting naltrexone were only \$7 million in 2007, while sales of disulfiram were about \$14 million. To put these numbers into perspective, the antidepressant Lexapro® (escitalopram oxalate), which was first FDA approved and marketed in the United States in 2002, had a sales volume of \$987 million in 2003 and \$1.7 billion in 2004 (IMS, 2007).

The average cost per prescription varied among alcoholism medications. Long-acting naltrexone was the most expensive at \$538 in 2006, reflecting the month-long duration of action due to its sustained release formulation. Acamprosate was the next most expensive at \$108 per prescription in 2006. Naltrexone is now available as a generic medication and, on average, costs \$100 per prescription. Disulfiram is the oldest alcoholism medication on the market and has long been off-patent; in 2006, it had an average cost per prescription of \$49. However, disulfiram's cost per prescription jumped to \$78 in 2007.

As shown in Table 2, in 2006, approximately 46% of prescriptions for acamprosate and about 51% of prescriptions for naltrexone were written by psychiatrists. In contrast, only 31% of disulfiram prescriptions were written by psychiatrists. Disulfiram is more widely prescribed by general practitioners than either naltrexone or acamprosate. General practitioners wrote 29% of acamprosate prescriptions, 25% of naltrexone prescriptions, and 42% of disulfiram prescriptions. Other practitioners prescribed alcoholism medications but to a lesser extent. For example, osteopathic medicine physicians prescribed 6% of naltrexone prescriptions, 8% of acamprosate prescriptions, and 10% of disulfiram prescriptions.

Opioid addiction medications

The number of prescriptions for the two buprenorphine formulations increased from 48,000 prescriptions in the year of their introduction (2003) to 1,910,000 prescriptions in 2007. Prescriptions of buprenorphine hydrochloride (Subutex®) increased from 9,000 in 2003 to 192,000 in 2007 (Table 1). Prescriptions of buprenorphine hydrochloride/naloxone (Suboxone®) increased from 39,000 in 2003 to 1,719,000 in 2007 (Table 1).

In 2007, sales of buprenorphine formulations reached \$327 million, with buprenorphine hydrochloride/naloxone making up 87% of the total. The average prices per prescription in 2007 were \$223 for buprenorphine hydrochloride, and \$166 for buprenorphine hydrochloride/naloxone, increases of more than 100% and 50%, respectively, since their introduction in 2003.

Most prescriptions for buprenorphine hydrochloride, prescribed during the initial phase of treatment, were written by primary care practitioners (34%), followed by psychiatrists

(28%), osteopathic specialists (12%), anesthesiologists (7%), and addiction medicine specialists (4%) in 2006 (Table 2). The majority of prescriptions for buprenorphine hydrochloride/naloxone, used for maintaining abstinence from opioid use, were also written by primary care practitioners (41%), followed by psychiatrists (28%), and osteopathic physicians (12%).

4. Discussion

The IMS data represent one of the most comprehensive sources available to track retail prescription medication sales at the national level. Nevertheless, the data have limitations. Because they are prescription-level data, the number of users for each medication and their adherence to the medication regimen are unknown. IMS data do not include information on the diagnosis for which the prescriptions were written, and it is possible that some of the prescriptions included in this analysis were for non-substance dependence conditions. Moreover, other medications, not included in this analysis, are used “off-label” to treat substance use disorders.

The data indicate that sales and prescriptions for medications to treat alcoholism and opioid dependence grew rapidly following the introduction of new medications. In the alcoholism medications market, the acceptance and use of acamprosate caused overall alcoholism medication sales to approximately double from 2002 to 2007. The introduction of a long-acting formulation of naltrexone and of acamprosate may have spurred an increase in oral naltrexone prescriptions, which had previously remained relatively steady. Buprenorphine sales grew even more rapidly and exceeded those of alcoholism medications by 2007.

Despite this growth, the number of individuals receiving pharmacotherapy continues to be small relative to the large number with substance use disorders. With 7.9 million people in the United States dependent on alcohol during the period 2001-2002 (Grant et al., 2004) and only 705,000 prescriptions filled for alcoholism medications in that year, at most, approximately 9% of the population needing alcoholism treatment received the equivalent of a single prescription of a medication approved to treat the disorder. Moreover, despite a large potential market, the current sales figure for alcoholism medications may not be large enough to engender focused interest and marketing dollars from industry. No addiction medication has become a “blockbuster drug” (i.e., achieving \$1 billion in sales in any year). Because pharmaceutical companies have historically based their business model on investment in medications with the potential for a large sales volume, the sales figures for alcoholism and opioid medications may be a deterrent to additional investment in the development and marketing of new alcoholism medications (Cutler, 2007; Gilbert, 2003; Cuatrecasas, 2006).

Prior research has found a variety of obstacles to greater adoption of substance dependence medications including physicians’ perceptions of limited effectiveness, difficulty “seeing” an impact of the medication, poor information dissemination, medication adverse effects, inadequate time available to physicians for patient management, patient reluctance to take medications, and high prices of medication (Mark et al., 2003a, 2003b, 2003c, Thomas et al., 2003). Substance abuse specialty provider characteristics that have been found to be positively associated with adoption of alcoholism medications include accreditation, physician employment by the facility, integrated patient care for co-occurring psychiatric conditions, more revenue from commercial insurance, and fewer linkages with the criminal justice system (Ducharme et al., 2006). Finally, in addition to these factors, reimbursement issues may be important barriers to the greater adoption of substance dependence medications. Horgan and colleagues (2008), using a nationally representative survey, found that 31% of private insurance products excluded buprenorphine from formularies and 55%

placed it on the highest cost-sharing tier. We are unaware of research that has examined Medicaid coverage of alcoholism medications or buprenorphine but clearly the extent of Medicaid coverage would influence utilization.

Another factor that is important to consider when parsing out the drivers of adoption is the level of marketing effort exerted by the pharmaceutical company. One hypothesis as to why Campral® (acamprosate) may have diffused more rapidly than ReVia® (naltrexone) is that Forest Laboratories has been more aggressive in disseminating information about acamprosate relative to the marketing effort by DuPont Pharmaceutical Company for naltrexone. In addition, the amount of prescribing by physician specialty may also have important policy implications. Mark and colleagues found that psychiatrists adopted new antipsychotic and alcoholism medications earlier than primary care practitioners (Mark et al, 2002, Mark et al, 2003). Consistent with this evidence, our data indicate that psychiatrists appear to have adopted acamprosate earlier than general practitioners. However, we did not find that the same was true for buprenorphine hydrochloride/naloxone prescribing, perhaps because some primary care practitioners may treat addicted patients without specializing in this area. One question for future studies is whether the specialty of the prescriber influences the nature of the treatment received, such as whether patients also receive the ancillary psychosocial services that are indicated when these medications are prescribed, and their degree of adherence with these medications.

The addition of new prescription medications to treat substance dependence offers additional treatment options for patients and may encourage a different patient population to obtain treatment than that traditionally found at substance abuse treatment facilities (Johnson, 2008; Kreek et al., 2005; Kreek et al., 2002; O'Brien, 2005). Research advances may contribute to the development of new substance dependence medications with enhanced effectiveness and safety profiles (Litten et al., 2005). The level of adoption by physicians of these new medications and the degree to which the pharmaceutical industry will pursue opportunities in this area, however, remains uncertain.

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Table 1

Alcoholism and Opioid Medication Prescriptions and Sales

	2003	2004	2005	2006	2007a	Average Annual Growth Rate
Substance Abuse Medications Combined						
Prescriptions (000)	441	713	1,240	1,848	2,631	42.9%
Sales Volume (\$) (000)	\$ 36,149	\$ 72,418	\$ 149,815	\$ 251,702	\$ 405,725	62.2%
Alcoholism Medications Combined						
Prescriptions (000)	393	405	563	674	720	12.9%
Sales Volume (\$) (000)	\$ 30,801	\$ 31,706	\$ 48,698	\$ 62,383	\$ 78,093	20.5%
Individual Alcoholism Medications						
Disulfiram (Antabuse)						
Prescriptions (000)	208	212	194	182	179	-3.0%
Percent of alcoholism prescriptions	53%	52%	34%	27%	25%	
Sales Volume (\$) (000)	\$ 9,031	\$ 9,307	\$ 8,542	\$ 8,832	\$ 13,904	9.0%
Cost per prescription (\$)	\$ 43	\$ 44	\$ 44	\$ 49	\$ 78	12.4%
Naltrexone (ReVia)						
Prescriptions	185	193	184	196	221	3.6%
Percent of alcoholism prescriptions	47%	48%	33%	29%	31%	
Sales Volume (\$) (000)	\$ 21,770	\$ 22,399	\$ 20,576	\$ 20,438	\$ 22,056	0.3%
Cost per prescription (\$)	\$ 118	\$ 116	\$ 112	\$ 104	\$ 100	-3.2%
Acamprosate (Campral)						
Prescriptions (000)			185	293	306	10.6%
Percent of alcoholism prescriptions			33%	43%	43%	
Sales Volume (\$) (000)			\$ 19,580	\$ 31,499	\$ 34,802	12.2%
Cost per prescription (\$)			\$ 106	\$ 108	\$ 114	1.4%
Long-Acting Injectable Naltrexone (Vivitrol)						
Prescriptions (000)				3	15	38.0%
Percent of alcoholism prescriptions				0.4%	2.1%	
Sales Volume (\$) (000)				\$ 1,614	\$ 7,332	35.4%
Cost per prescription (\$)				\$ 538	\$ 489	-1.9%
Opioid Medications Combined						
Prescriptions (000)	48	308	677	1,174	1,911	108.9%

	2003	2004	2005	2006	2007a	Average Annual Growth Rate
Sales Volume (\$ (000))	\$ 5,348	\$ 40,712	\$ 101,117	\$ 189,319	\$ 327,632	127.7%
Individual Opioid Medications						
Buprenorphine HCl (Subutex)						
Prescriptions (000)	9	49	84	136	192	84.4%
Percent of opioid prescriptions	19%	16%	12%	12%	10%	
Sales Volume (\$)	\$ 1,005	\$ 6,483	\$ 14,373	\$ 27,324	\$ 42,780	111.7%
Cost per prescription (\$)	\$ 112	\$ 132	\$ 171	\$ 201	\$ 223	14.8%
Buprenorphine HCl/naloxone (Suboxone)						
Prescriptions (000)	39	259	593	1,038	1,719	113.2%
Percent of opioid prescriptions	81%	84%	88%	88%	90%	
Sales Volume (\$)	\$ 4,343	\$ 34,229	\$ 86,744	\$ 161,995	\$ 284,852	130.9%
Cost per prescription (\$)	\$ 111	\$ 132	\$ 146	\$ 156	\$ 166	8.3%

a. Projected based on data through August 2007

Table 2
Alcoholism and Opioid Medication Prescriptions by Physician Specialty, 2002–2006

	2002	2003	2004	2005	2006
Alcoholism					
Naltrexone					
Psychiatry	47%	54%	52%	50%	51%
Family, Internal, General	17%	24%	25%	26%	25%
Osteopathic Medicine	6%	6%	6%	6%	6%
Nurse Practitioner	2%	3%	3%	4%	5%
Other ¹	29%	13%	14%	15%	13%
Acamprosate					
Psychiatry				51%	46%
Family, Internal, General				27%	29%
Osteopathic Medicine				8%	8%
Nurse Practitioner				4%	6%
Other ²				6%	6%
Unspecified or Unknown				4%	4%
Disulfiram					
Family, Internal, General	39%	43%	43%	43%	42%
Psychiatry	26%	30%	31%	30%	31%
Osteopathic Medicine	11%	10%	10%	10%	10%
Nurse Practitioner	3%	3%	3%	4%	4%
Physician Assistant	3%	3%	3%	4%	4%
Other ³	6%	6%	5%	6%	6%
Unspecified or Unknown	12%	4%	3%	3%	3%
Naltrexone IM					
Psychiatry					100%
Opioid Addiction					
Buprenorphine HCl/naloxone (Suboxone)					
Family, Internal, General		42%	42%	42%	41%
Psychiatry		31%	29%	29%	28%

	2002	2003	2004	2005	2006
Osteopathic Medicine					
Addiction Medicine		11%	9%	11%	12%
Anesthesiology		8%	6%	4%	2%
Other ⁴		3%	2%	2%	2%
Unspecified or Unknown		-	7%	9%	11%
Buprenorphine HCl (Subutex)					
Family, Internal, General		6%	3%	3%	3%
Psychiatry		33%	36%	34%	34%
Osteopathic Medicine		33%	31%	30%	28%
Anesthesiology		11%	13%	11%	12%
Addiction Medicine		11%	9%	6%	7%
Other ⁵		11%	7%	5%	4%
Unspecified or Unknown		-	2%	11%	13%
		-	2%	2%	2%

¹ Includes neurology, pediatrics, physician assistant, addiction medicine, anesthesiology, obstetrics/gynecology, other physician specialties, and unspecified or unknown physician specialties.

² Includes physician assistant, addiction medicine, emergency medicine, neurology, geriatrics, anesthesiology, and other physician specialties.

³ Includes emergency medicine, addiction medicine, cardiology, geriatrics, and other physician specialties.

⁴ Includes emergency medicine, physical medicine and rehab, general surgery, obstetrics/gynecology, and other physician specialties.

⁵ Includes obstetrics/gynecology, neurology, general surgery, urology, emergency medicine, physical medicine and rehab, and other physician specialties.

EXHIBIT 7

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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- Patent listings published prior to August 18, 2003, only identify method-of-use claims. The listed patents may include drug substance and/or drug product claims that are not indicated in the listing.
- As of December 5, 2016, an NDA holder submitting information on a patent that claims both the drug substance and the drug product (and is eligible for listing on either basis) is required only to specify that it claims either the drug substance or the drug product. Orange Book users should not rely on an Orange Book patent listing, regardless of when first published, to determine the range of patent claims that may be asserted by an NDA holder or patent owner.

Patent and Exclusivity for: N209819

Product 001

BUPRENORPHINE (SUBLOCADE) SOLUTION, EXTENDED RELEASE
100MG/0.5ML (100MG/0.5ML)

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested
001	10198218	06/06/2031			U-2489	
001	8921387	01/06/2032		DP	U-2173 U-2174	
001	8975270	09/05/2031		DP	U-2175 U-2206	
001	9272044	06/06/2031			U-2176 U-2177 U-2178 U-2209	
001	9498432	06/06/2031		DP	U-2179	
001	9782402	06/06/2031		DP	U-2176 U-2180 U-2207 U-2208	
001	9827241	06/06/2031		DP	U-2174 U-2181 U-2206 U-2210 U-2211	

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	NP	11/30/2020

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EXHIBIT 8

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Review of Request for Orphan-Drug Designation

Date of request: November 8, 2004
Date received by FDA: November 9, 2004
Dates of Amendments: January 19, February 22, May 24 and 25,
June 8 and 10, 2005
Date review completed: May 20, 2005
Designation request: (b) (4)
Generic Name: Raloxifene
Trade Name: Evista®
Sponsor: Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285
Contact: David R. McAvoy, J.D., M.S.E.S.
Director
Office of Scientific and Regulatory Affairs
Lilly Research Laboratories
Eli Lilly and Company
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Global Regulatory
Eli Lilly and Company
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Drug manufacturer: Eli Lilly
Proposed designation: Reduction of risk of breast cancer in
postmenopausal women.
Regulatory status:

Evista is marketed for the prevention and treatment of osteoporosis in the U.S. (NDA 20-815), Europe, Canada, Japan, and 103 other countries. Evista is being developed for breast cancer risk reduction under (b) (4) (FDA Division of Oncology Drug

Products). The IND was submitted to the FDA in October 1998. No supplemental NDA has been submitted to FDA for Evista for breast cancer risk reduction in postmenopausal women. Evista is not currently approved for breast cancer risk reduction in the U.S., but has recently been approved for reducing the risk of breast cancer in postmenopausal women with osteoporosis in Philippines, South Africa, Venezuela, and Argentina; for prevention of breast cancer in postmenopausal women with osteoporosis in Mexico, Russia, and Turkey; and for both reducing the risk and prevention of breast cancer in Lebanon.

1. Disease/Condition Background

Breast cancer is a malignant proliferation of epithelial cells lining the ducts or lobules of the breast and is the most common cause of cancer in women. Each year, 182,000 cases of breast cancer and 43,300 deaths occur in the United States. Risk factors include family history, nulliparity, early menarche, advanced age, and a personal history of breast cancer (in situ or invasive). The presence of certain genetic mutations has also been associated with breast cancer, including BRCA-1 and BRCA-2 mutations.

Various combinations of surgery, radiation therapy, chemotherapy, and hormone therapy treatment options are currently employed in the treatment of breast cancer. In addition, much interest has emerged in the area of chemoprevention, using natural and synthetic compounds to intervene in the early stages of cancer (before invasive disease begins), with the intention to reverse, suppress, or prevent the progression of premalignant lesions to invasive carcinoma.

The Breast Cancer Prevention Trial (BCPT or the National Surgical Adjuvant Breast and Bowel Project [NSABP] P-1 trial) demonstrated that, in women at high risk of breast cancer, tamoxifen citrate significantly reduced the risk of invasive breast cancer.¹ It is theorized that raloxifene also may reduce the risk of invasive breast cancer and do so with a potentially more favorable risk profile than tamoxifen. Ongoing research is being conducted to demonstrate the efficacy and safety of Evista in such a chemoprevention context for the purpose of securing approval of a new indication.

While early detection with effective treatment has reduced mortality in some groups of women with breast cancer, efforts to control this disease by encouraging the development of primary prevention strategies continue. Currently, only tamoxifen is approved in the U.S. for the reduction of risk of breast cancer.

U.S. approval of the tamoxifen chemoprevention indication was based on the NSABP P-1 trial. The P-1 trial was a double-blind, randomized, placebo-controlled trial with the primary objective of determining whether 5 years of treatment with tamoxifen 20 mg/day would reduce the incidence of invasive breast cancer in women at high risk for the disease. The median duration of treatment at study termination was 3.5 years. After a total of 4.2 years of follow-up since enrollment, the relative risk for invasive breast cancer with tamoxifen treatment, compared with placebo for women 60 years of age or

(b) (4)

older, was 0.45 (95% Confidence Interval [CI] 0.27, 0.74). The absolute risk reduction for invasive breast cancer with tamoxifen therapy was 3.4%.¹

Tamoxifen is registered in the U.S. for "reduction of the risk of breast cancer in women at high risk of the disease," where "high risk" is defined as a 5-year risk of invasive breast cancer greater than 1.7% (the average risk for a woman 60 years of age), based on the Gail Risk Evaluation.² Tamoxifen is a first-generation selective estrogen receptor modulator (SERM) that can have estrogen agonist effects on bone and uterine tissues, and can have estrogen antagonist effects on breast tissue.

2. Population Estimate

To qualify raloxifene as an orphan drug, the sponsor contends that there is no reasonable expectation that costs of research and development of the drug for reduction of risk of breast cancer in postmenopausal women can be recovered by sales of the drug in the U.S.

(b) (4) However, the sponsor states that they reserve the right to request orphan designation under the alternative standard of estimated patient population (21 CFR 316.20(b)(8)(i)), if necessary.

The sponsor states that the planned indication of raloxifene for breast cancer risk reduction in postmenopausal women represents a legitimate patient population. The sponsor notes that raloxifene is contraindicated for premenopausal women.

Reviewer Comment:

Raloxifene is classified as FDA pregnancy category X. It is contraindicated in women during pregnancy or in women who may become pregnant. Currently, raloxifene is not indicated for use in premenopausal females. Safety has not been established and its use is not recommended in this population. In addition, raloxifene should be avoided in women who are breast-feeding due to the potential risk to the newborn, although it is not known if the drug is excreted in human milk. Therefore, it remains reasonable for the sponsor to limit analyses included in this designation request to postmenopausal women.

3. Rationale for Use

Raloxifene is a selective estrogen receptor modulator (SERM) of the benzothiophene class. Raloxifene produces estrogen-like effects on bone and lipid metabolism, while antagonizing the effects of estrogen on the breast and uterus. The tissue-selective estrogen agonist and antagonist effects of raloxifene reside with the high affinity interaction for estrogen receptors. The ability of raloxifene to compete with estrogen for estrogen receptor binding is believed to account for the estrogen-antagonist effects in breast and uterus tissue, whereas the high affinity interaction of raloxifene with estrogen receptor in bone, vascular, and hepatic tissue is believed to produce estrogen-like effects of reduced resorption of bone, vasodilation, and lowered serum cholesterol.

Large clinical trials examining the long-term effects of raloxifene include the Raloxifene Use for the Heart (RUTH) study, the Multiple Outcomes of Raloxifene Evaluation (MORE) that evaluates effectiveness for osteoporosis and the effect of raloxifene therapy on the risk of cardiovascular events and breast cancer in postmenopausal women up to 80 years of age, and the Study of Tamoxifen and Raloxifene (STAR) study that is designed to compare efficacy in the prevention of breast cancer. These studies include more than 35,000 women over almost a decade of research and will provide a substantial clinical experience from which to evaluate the effectiveness and safety of Evista for breast cancer risk reduction.

The Multiple Outcomes of Raloxifene Evaluation (MORE), a randomized, double-blind trial evaluated 7,705 postmenopausal women with osteoporosis. The effect on breast cancer incidence was a secondary endpoint. After a median follow-up of 47 months, the risk of invasive breast cancer decreased by 72%.³ The incidence of all types of breast cancer (regardless of invasiveness) was reduced with raloxifene by 62%, corresponding to a relative risk of 0.38 (95% CI 0.24-0.58). This study also reported a 72% reduction in relative risk of invasive breast cancer with raloxifene (RR = 0.28, 95% CI 0.17-0.46). These data indicate that 93 osteoporotic women would need to be treated with raloxifene for 4 years to prevent one case of invasive breast cancer. As with tamoxifen, raloxifene appeared to reduce the risk of estrogen receptor-positive breast cancer but not estrogen receptor-negative breast cancer. Similar to tamoxifen, raloxifene is associated with an excess risk of hot flashes and thromboembolic events. The risk of venous thromboembolic disease (deep venous thrombosis or pulmonary embolism) was 2.4 times higher in women assigned to the raloxifene groups than to the placebo group. No excess risk of endometrial cancer was observed after 47 months of follow-up. Raloxifene did not increase the risk of endometrial hyperplasia. Subgroup analyses after 4 years of follow-up suggest that, among women who have osteoporosis, raloxifene reduces breast cancer incidence for both women at higher and lower risk of developing breast cancer. It is not known if women without osteoporosis would benefit in the same way.

4. Cost Recovery Analysis

The sponsor contends that there is no reasonable expectation that costs of research and development of the drug for reduction of risk of breast cancer in postmenopausal women can be recovered by sales of the drug in the U.S.

As stated in the sponsor's executive summary, costs and revenues were subjected to agreed-upon procedures by an independent certified public accountant (b) (4) as required by FDA regulations. Costs were calculated in accordance with Generally Accepted Accounting Principles (GAAP). Projected revenues attributable to the breast cancer risk reduction indication were based on primary market research with a sample of U.S. physicians most likely to prescribe Evista and who will be targeted by the company for marketing after the new indication is approved. Lilly calculated these revenues on an all-inclusive basis, which captures the total impact of the new indication on the U.S. sales of Evista.

(b) (4)

The financial analysis is set forth in a product contribution statement prepared by Lilly, entitled, "Statement of Historical and Projected Product Contribution Assuming Generic Entry Would Occur In 2012 Without Breast Cancer Risk Reduction Indication, Generic Entry Would Occur In 2010 With Breast Cancer Risk Reduction Indication and Incremental Net Sales of (b) (4)"

The following assumptions and allocations are contained in this product contribution statement:

Discounting

- 1) *Present value* was used to measure revenue and expenses. The product contribution each year was discounted to present value using the sponsor's weighted average cost of capital (WACC).

Costs

- 2) Research and Development (R&D) costs include both indication-specific costs and "common" costs.
 - a) For indication-specific costs, preclinical and clinical development efforts associated with both breast cancer treatment and breast cancer risk reduction were included. In order to be included in the indication-specific cost estimate, clinical studies had to have a breast cancer-related primary endpoint.
 - b) Common costs include discovery, clinical pharmacology, general safety studies, and formulation development and were allocated based on the number of indications taken into Phase 3 development at the time of the orphan drug application (b) (4)
- 3) The percentage of development costs incurred outside the U.S. was estimated using sampling. An expense was considered foreign if cash payment was made by a non-US affiliate. All expenses paid by the U.S. affiliate were considered domestic costs, although a portion of such payments may have been made for work done outside the United States.
- 4) Cost estimates for manufacturing, distribution, marketing, selling, and general and administrative expenses rely on the assumption that the sponsor's future sales to expense ratios will be consistent with past ratios. These costs were calculated as a percent of sales and applied to the sponsor's projected revenue for the breast cancer risk reduction indication.

Revenue

- 5) Revenue is calculated from the sale of the drug in the U.S. during its first 7 years of marketing for the orphan indication and assumes that orphan exclusivity has not been granted.

- 6) Projected revenue includes sales driven by the breast cancer risk reduction indication as well as sales driven by a combination of the breast cancer risk reduction indication and existing osteoporosis indications.
- 7) The sponsor assumes Evista will face generic competition in 2010 if it adds a breast cancer risk reduction indication to its label in 2007, because it is very unlikely that Evista will have patent protection for this new use. Under this assumption, the only U.S. intellectual property protection for the breast cancer risk reduction indication would be data package exclusivity (also known as "Hatch-Waxman exclusivity") which will expire 3 years after approval of Evista by FDA for this new indication.
- 8) The current approved uses (prevention and treatment of osteoporosis) are protected by three use patents in the U.S., two that expire on July 28, 2012 and one that expires on March 2, 2014. The sponsor is assuming that only the 2012 use patents will be found valid and enforceable.
- 9) Market research was performed using (b) (4) to survey (b) (4) U.S. physicians (primary care and obstetrician-gynecologist physicians) who will be the target of the sponsor's marketing efforts.
- 10) Market research assumed a (b) (4) invasive breast cancer risk reduction in postmenopausal women versus placebo, and identical safety profile to the current Evista label.
- 11) Year-on-year market uptake projections were based on the rate observed with the weekly formulation of Actonel (risedronate) as well as the uptake rate observed with Zyprexa for bipolar mania. Decay rate was based on the rate of decline observed when generic competition for Prozac entered the U.S. market.
- 12) Market research results were combined with Lilly projections about the size of the U.S. osteoporosis market, expected entrants to the U.S. market, and market share distribution to generate an incremental prescription (and ultimately sales) impact of the breast cancer risk reduction indication for Evista.
 - a) The sponsor developed a 7-year prescription projection for Evista with a breast cancer risk reduction indication using the (b) (4) research (see item 9 above) and uptake and decay rates (see item 11 above). The projection was compared to a projection of Evista prescriptions without a breast cancer risk reduction indication, but with the longer period of market exclusivity that Evista would maintain absent that indication (2012 versus 2010, see items 7 and 8 above), to calculate the total incremental prescriptions associated with the breast cancer risk reduction indication.
 - b) The sponsor assumes that Evista is competing in the osteoporosis market, which was selected given (b) (4) data that indicated that the breast cancer risk reduction indication incremental prescriptions are principally attributable

(b) (4)

to osteoporosis. Market size projection is based on extrapolation of historical market growth, assuming that the growth rate for this maturing market will slow in the future.

- c) Evista's market share is projected to decline in the osteoporosis market. Five new product launches for osteoporosis between now and 2007 were modeled for this projection. The sponsor projects that the launch of the breast cancer risk reduction indication in 2007 will moderately grow Evista's U.S. market share from the 2006 level.

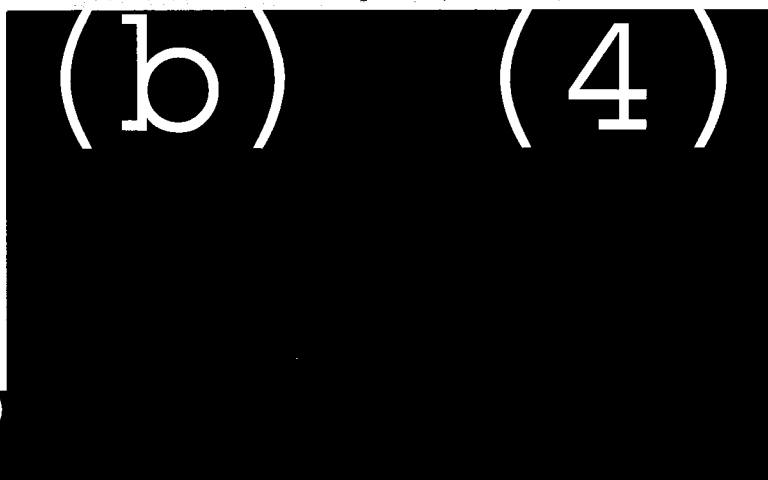
13) The sponsor assumes an average (b) net price growth from 2003 until 2006, with less than (b) price growth after 2006 as new osteoporosis products enter the market. The price is the same with or without the breast cancer risk reduction indication.

14) The sponsor assumes that Evista marketing and selling effort is comparable to 2003 Evista marketing and selling effort in the U.S., with the addition of direct-to-consumer advertising.

The sponsor estimates the development and marketing present value costs for the new indication at (b) (4) (non-discounted price (b) (4)). Lilly projects total revenue attributable to this indication in the U.S. of (b) (4) for the 7-year post-approval period required for an orphan designation analysis. The result is that the sponsor's expected loss is more than (b) (4) (all amounts in 2004 present value). Without factoring in the time value of money, Lilly's expected loss on this indication totals more than (b) (4) if an orphan designation is not granted.

The following pie chart shows distribution of the cumulative present values of expenses:

Cumulative Present Value of Expenses (1991-2013)



The sponsor attempts to validate this projected loss with the results of five separate sensitivity analyses, conducted to assess the impact of changing key assumptions that

(b) (4)

underlie the revenue projection. The sponsor contends that data from these analyses support their cost recovery analysis findings even if: 1) the expected price of Evista is increased to levels that could not be justified in today's competitive market; 2) the expected approval date for the new indication is delayed or accelerated by several years; 3) the expected period of market exclusivity based on existing patents is modified; 4) the expected market size is increased beyond what historical experience would suggest is feasible; or 5) the incremental prescription projection for Evista is increased by an amount that represents the largest variance between projected and actual prescribing based on the historical accuracy of the market research firm utilized by the sponsor to conduct that research.

The January 19, 2005 amendment provides additional information regarding the cost recovery analysis:

1) New competition sensitivity analysis.

Holding all other factors constant, the sponsor was unable to identify any future competitive environment that enables the company to break even on its breast cancer risk reduction investment. The sponsor modeled scenarios ranging from no new competition to new competition completely dominating the market. As discussed in the application, the sales attributable to the breast cancer risk reduction indication are calculated based on the difference between Evista sales with and without this indication. In the absence of new competition, sales of Evista without the breast cancer risk reduction indication would be substantially greater and the difference in sales between the "with" and "without" scenarios would be decreased. As a result, the sales attributable to the breast cancer risk reduction indication would be decreased, and Lilly's net loss on its breast cancer risk reduction investment would be increased. In a more competitive environment, Lilly's loss on the breast cancer risk reduction indication would be reduced but not eliminated. In this case, sales of Evista in 2006 would be smaller, thus providing a smaller base from which to grow with the new indication.

In the case of no new competition, the present value of sales attributable to the breast cancer risk reduction indication is less than (b) (4). Using the base case (as presented in the original designation), with five new entrants, the present value of sales attributable to the breast cancer risk reduction indication sales is (b) (4). Lilly views this case as the most likely. In the case that new competition dominates the market, the present value of sales attributable to the indication is (b) (4).

(b) (4)

2) Market Research

The sponsor provided additional information regarding the market research conducted by (b) (4). Table 1 presents the results of this research:

Table 1. Expected Year 1 Prescriptions (millions)

	Control Physicians		BrCa Physicians	
	Base Evista Rx'ing (Year 1 Rx MM)		Evista Rx'ing without Product X	Evista Rx'ing with Product X
Total PCPs	(b) (4)		(b) (4)	(b) (4)
for Osteoporosis				
for Breast Cancer Prevention Only				
Total Ob/Gyns				
for Osteoporosis				
for Breast Cancer Prevention Only				
Total All MDs				
for Osteoporosis				
for Breast Cancer Prevention Only				
DTC Driven			(b) (4)	

All responses indicate Rx's in year 1 (millions)

Sample Physicians			
	Control	BrCa without Prod X	BrCa with Prod X
PCPs	(b) (4)		
OB/Gs			
Control Physicians see only the current Evista message			
BrCa Physicians without Prod X see only Evista + BrCa Risk Reduction message			
BrCa Physicians with Prod X see both Evista + BrCa RR and Product X message			

Abbreviations: BrCa = breast cancer, DTC = direct-to-consumer, MDs = doctors, MM = millions,
Ob/Gyns = obstetrician/gynecologists, PCPs = primary care physicians, Rx = prescription.

3) Research and Development costs

The sponsor provided additional information regarding the studies (both indication-specific and common) included in the research and development costs.

4) Third Party Grants

The sponsor defines a third party grant as a payment by the company to an individual researcher or research organization for clinical work related to the studies. The sponsor states that the research and development expenses included in the orphan drug financial analysis include only Lilly expenses. Expenses incurred or funded by government entities or other third parties are not included.

(b) (4)

5) Financials

The sponsor provides additional information on Product Cost Schedule, Manufacturing Variance Schedule, Distribution Cost Schedule, Research and Development Cost Schedule, General and Administrative Expense Schedule, and Selling and Marketing Expense Schedule supporting the product contribution statement provided in the initial application. Also included is the (b) (4) report detailing the derivation of Lilly's historical weighted average cost of capital (WACC) and the (b) (4) report providing Lilly's current WACC.

The February 22, 2005 amendment provides additional information regarding the cost recovery analysis:

- 1) The sponsor provided additional information regarding: the methodology involved in calculating the (b) increase in first year prescriptions; The (b) (4) Marketing Research database; and the capture of any tamoxifen market.
- 2) The sponsor states that the reason for the difference between the survey results and actual prescription numbers available in the (b) database is due to the fact that this estimate is projected to 2006.
- 3) Regarding overstatement of prescription patterns, (b) (4) relies on "proprietary techniques" that are not discussed in detail. (b) (4) uses a calibrated model to provide a forecast for expected sales given a dual indication Evista. The stated accuracy of this model to evaluate changes to established brands is within (b) (versus (b) for new product models). (b) (4) states that this design is standard for this type of research within the industry.
- 4) PCPs/OB-GYNs make up (b) of the osteoporosis market. Doctors in decile 3 to 10 (i.e., 3+ decile) include (b) of the prescription writing universe. This is standard (b) (4) sampling.
- 5) (b) (4) was unable to differentiate between prevention and treatment for tamoxifen. In response, Lilly decided to use (b) (4) to estimate usage in primary prevention, which found that (b) of tamoxifen was for prevention ((b) (4)).
- 6) The doctor survey collected data on:
 - Current prescription behavior
 - Expected prescription behavior post the new indication
 - Attribute ratings versus other treatment offerings
 - Likelihood of increasing prescription activity post the new introduction
 - Open-ended likes/dislikes/confusion
 - Closed-ended uniqueness and believability
 - Writing behavior vis-à-vis indication (osteoporosis, cancer prevention)
 - Perceptual changes due to new indication

7) Consumer survey collected data on:

- Current category experience
- Classification (e.g., is the respondent 'at risk'?)
- Consumer likelihood to take action on the DTC message
- Types of action consumer would take
- Expected speed of action
- Open-ended likes/dislikes/confusion
- Closed-ended uniqueness and believability
- Other diagnostics

5. Evaluation and Recommendation

The sponsor requests orphan-drug designation for raloxifene (Evista®) for reduction of risk of breast cancer in postmenopausal women. Based on the information presented, the sponsor has provided sufficient evidence to support the scientific rationale for the use of raloxifene in this patient population. However, concerns remain regarding the cost recovery analysis intended to support the sponsor's contention that there is no reasonable expectation that costs of research and development of the drug can be recovered by sales of the drug in the U.S.

To assist in the review of the economic and market research components of this complex cost recovery analysis, OOPD consulted with FDA's Office of Economics Staff (John Goldsmith, Ph.D.) and with a Special Government Employee working with FDA's Division of Drug Marketing, Advertising, and Communications (Jack Swasy, Professor of Marketing at American University). These consult reviews are included in the file.

At issue with the cost recovery analysis are the numerous assumptions which the sponsor relies upon to justify the proposed financial loss without orphan-drug designation. While some of these assumptions appear appropriate, several others remain quite speculative. These remaining concerns and questions include:

1. The sponsor is actively litigating patent infringement cases (both primary and secondary patents). If successful, generic entry could be delayed until 2017, regardless of indication. This assumption is critical to the sponsor's current analysis. As stated in the original application (page 29, footnote 16) the sponsor has assumed for the purpose of this request that one or more generic companies may ultimately circumvent these other patents. This assumption is grounded on the Federal Trade Commission's statistical analysis of generic patent challenges and is not based upon the sponsor's assessment of the possible outcomes of the existing challenge to its Evista Orange Book patents. The sponsor has taken the position in connection with existing generic drug litigation involving Evista Orange Book patents that these other patents are infringed and validly enforceable beyond 2012, as evidenced by the following statements in their 2003 Annual Report filed with the Securities and Exchange Commission:

(b) (4)

"In October 2002, we were notified that Barr Laboratories, Inc. (Barr), had submitted an ANDA to the U.S. FDA seeking permission to market a generic version of Evista several years prior to the expiration of our U.S. patents covering the product, alleging that the patents are invalid or not infringed. On November 26, 2002, we filed suit against Barr in federal district court in Indianapolis seeking a ruling that Barr's challenges to our patents claiming the method of use and pharmaceutical form (expiring from 2012 to 2017) are without merit. In June 2003, Barr added a challenge to one of our additional patents (expiring in 2017), claiming a component in the pharmaceutical form of Evista. This patent has now been added to the lawsuit. The trial is tentatively scheduled to begin in August 2005. While we believe that Barr's claims are without merit and expect to prevail, it is not possible to predict or determine the outcome of the litigation. Therefore, we can provide no assurance that we will prevail. An unfavorable outcome could have a material adverse impact on our consolidated results of operations, liquidity, and financial position."⁴

2. How accurate and robust is the market research performed by (b) (4)?
3. How accurate are the uptake/decay rates?
4. How might "marketing and selling effort" affect the analysis? The level of marketing expense assumes the same level as in 2003 plus direct to consumer spending. This issue is further explained in Jack Swasy's consult review.
5. Is it appropriate to assume the price is not likely to increase significantly?
6. How accurate is the market size/share estimate?
7. Is the "summary of significant projection assumptions" (SSPA) reasonable and accurate?
8. Is the assumption of "5 new product launches between now and July 2007" provided in the SSPA accurate?
9. Is price growth rate appropriate as described in the SSPA?
10. The doctor and consumer surveys use "Product X," a SERM with better bone efficacy, an additional indication for female sexual arousal disorder, but no breast cancer risk reduction. This product profile was selected based on 3 SERMS in late stage development. However, it is unclear that this comparator is the most appropriate approach at estimating the impact of a new indication which could potentially differentiate Evista from all other products on the market or in clinical development.
11. It remains unclear whether (b) (4) "normalization" procedure based on historical trends applies to this specific example. No detailed explanation is given for how this

normalization is validated for Evista's particular situation, given the addition of a second indication.

Because these issues raise questions about the cost recovery analysis, it has been difficult to determine whether these assumptions meet the threshold for presenting a reasonably likely scenario for purposes of orphan-drug designation. However, after considering all the information presented in this request, it is this reviewer's opinion that the sponsor has presented available documentation that supports their contention that there is no reasonable expectation that costs of research and development can be recovered by sales in the U.S., as required under 21 CFR 316.21(c). However, before a recommendation to grant this request can be proposed, it is recommended that the sponsor be required to provide written commitments which detail the sponsor's understanding regarding reporting requirements intended to substantiate the assumptions and hypotheses presented in this request. This information should be presented in subsequent annual reports, as required under 21 CFR 316.30, as well as prior to marketing approval, and after a certain period of postmarketing experience is available (to be negotiated). At each of these time points, OOPD will need to determine if the designation and/or marketing exclusivity should remain in place or whether the designation and/or exclusivity should be revoked as permitted under 21 CFR 316.29.

This recommendation appears to be supported by the following regulations:

1. 21 CFR 316.21(d): A sponsor that is requesting orphan drug designation for a drug designed to treat a disease or condition that affects 200,000 or more persons shall, at FDA's request, allow FDA or FDA designated personnel to examine at reasonable times and in a reasonable manner all relevant financial records and sales data of the sponsor and manufacturer.
2. 21 CFR 316.29 (Revocation of orphan drug designation):
 - (a) FDA may revoke orphan drug designation for any drug if the agency finds that:
 - (1) The request for designation contained an untrue statement of material fact; or
 - (2) The request for designation omitted material information required by this part; or
 - (3) FDA subsequently finds that the drug in fact had not been eligible for orphan drug designation at the time of submission of the request therefor.
 - (b) For an approved drug, revocation of orphan drug designation also suspends or withdraws the sponsor's exclusive marketing rights for that drug but not the approval of the drug's marketing application.

(b) (4)

3. 21 CFR 316.30(c): A brief discussion of any changes that may affect the orphan-drug status of the product.

It is recommended that this review and recommendation, as well as any subsequent written responses from the sponsor on this issue, be forwarded to FDA's Office of General Counsel before a final decision on this request is made.

In addition, the sponsor has stated their intention to respond to four issues raised in Jack Swasy's review (dated May 18, 2005), and submit this response as an amendment to the request. This information should be forwarded to Prof. Swasy for his consideration.

Also, the (b) (4) report will need to be finalized and submitted as an amendment. This report should be provided to John Goldsmith for his consideration and approval.

Assuming these outstanding issues are adequately addressed, it is recommended that the following letter comments (in addition to boiler-plate language) be used as a template when drafting a designation letter to be issued to the sponsor (these comments should be edited based on pending sponsor commitments and other agreements):

Reference is made to your request for orphan-drug designation dated November 8, 2004, for raloxifene (Evista®) for breast cancer risk reduction in postmenopausal women. We also refer to our acknowledgement letter of November 10, 2004, and to your submissions dated January 19, February 22, May 24 and 25, June 8 and June 10, 2005.

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your request for orphan drug designation of raloxifene (trade name Evista®) is granted for reduction of the risk of breast cancer in postmenopausal women. Specifically, orphan-drug designation is being granted on the basis that there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States for seven years after approval of a marketing application [21 CFR 316.20(8)(ii)].

We acknowledge your agreement to provide additional information as described in your commitment letter of June 10, 2005, and as outlined below.

1. Provide updated information related to the assumptions on patent status reflected in section 8.4.2 of your Application. This includes information on any new patents or other significant intellectual property rights that would impact Evista for the orphan indication.
2. Provide information identifying new competitor product launches since the date of application (section 8.4.5.2).
3. Provide a current and projected net price for the next 12-month period for Evista.

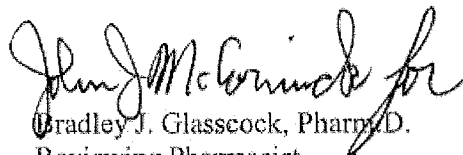
(b) (4)

4. Provide updated estimates for projected marketing investment for the orphan indication as reflected in section 3.2, Supplement #1 of the Application.
5. Provide a description of Evista's prescription growth for the previous 12-month period and, for the first report, compare to the 12-month period immediately prior to launch.
6. Provide Evista's net revenue for the previous 12-month period and, for the first report, compare to the 12-month period immediately prior to launch.

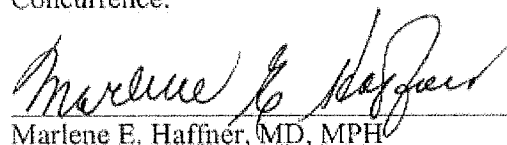
As agreed to in your June 10, 2005 letter, the above information will be submitted within 90 days following the first full year of marketing Evista for the orphan indication in the United States, and thereafter annually for an additional two years.

It should be noted that this Office reserves the right to revoke the orphan drug designation of Evista, and exclusive marketing rights if approved, as stipulated under 21 CFR 316.29.

If you have any questions, please contact Jeff Fritsch, R.Ph., in this Office at (301) 827-3666.


Bradley J. Glascock, Pharm.D.
Reviewing Pharmacist
OOPD/FDA/HF-35

Concurrence:



Date: 17 June 2005

Marlene E. Haffner, MD, MPH
RADM, USPHS
Director, Office of Orphan Products Development

cc:

HF-35/Designation file (b) (4)
HF-35/Chron file
HF-35/Glascock

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EXHIBIT 9

February 14, 2019

FY 2018 Adjusted Financial Results In-Line with Guidance. FY 2019 SUBLOCADE™ Guidance Introduced.

Period to December 31st	Q4 2018 \$m	Q4 2017 \$m	% Δ Actual FX	% Δ Constant FX	FY 2018 \$m	FY 2017 \$m	% Δ Actual FX	% Δ Constant FX
Net Revenue	236	265	-11	-10	1,005	1,093	-8	-9
Operating Profit/(Loss)	20	(115)	*	*	292	193	+51	+48
Net Income/(Loss)	24	(145)	*	*	275	58	*	*
EPS/(Loss) (cents per share)	3	(20)	*	*	38	8	*	*
Adjusted Operating Profit ¹	78	70	+11	+10	332	403	-18	-19
Adjusted Net Income ¹	67	54	+24	+22	272	270	+1	-
Adjusted EPS ¹	9	7	+29	+22	37	37	-	-

¹Adjusted basis excludes the impact of exceptional items as referenced in Notes 3 and 4. * Not meaningful.

The Release Contains Inside Information

Full Year 2018 Financial Highlights

- Net revenue of \$1,005m, a decrease of 8% versus prior year (-9% at constant exchange). U.S. market growth was more than offset by U.S. SUBOXONE® Film share loss, targeted rebating and mix impact from growth in government channels (Medicaid).
- Operating profit was \$292m (FY 2017: \$193m). On an adjusted basis, FY 2018 operating profit was \$332m, a decrease of 18% (Adj. FY 2017: \$403m). Lower net revenue and higher SUBLOCADE™ and PERSERIS™ launch investments were partially offset by impacts from operating expense reductions.
- Net income was \$275m (FY 2017: \$58m). On an adjusted basis, FY 2018 net income was \$272m +1% (Adj. FY 2017: \$270m). Lower adjusted operating profit was more than offset by lower net financing costs and effective tax rate.
- Cash balance at FY 2018 of \$924m (+\$61m). Net cash of \$681m (+\$305m). Voluntary repayments of \$235m on the Term Loan were made in the period; \$243m remains outstanding.

Key Operating Developments

- U.S. SUBOXONE® Film market share averaged and exited FY 2018 at 53%.
- The Court of Appeals for the Federal Circuit (CAFC) has denied Indivior's motion for rehearing and rehearing *en banc* following the CAFC's ruling vacating the preliminary injunction (PI) granted against Dr. Reddy's Laboratories (DRL). The CAFC has also denied Indivior's emergency motions with the CAFC to stay issuance of the mandate pending resolution of Indivior's appeal of the District of Delaware's decision finding DRL does not infringe U.S. Patent No. 8,603,514 ("the '514 patent"), and pending Indivior's forthcoming petition for a writ of certiorari to the Supreme Court of the United States in the PI matter. The CAFC has ordered issuance of the mandate on February 19, 2019. In response, Indivior will file a petition with the Supreme Court of the United States to stay the mandate pending the outcome of the forthcoming petition for certiorari seeking to overturn the CAFC's PI vacatur. If the mandate issues, Indivior assumes that DRL and Alvogen Pine Brook LLC will launch their generic buprenorphine/naloxone sublingual film products on an "at-risk" basis, leading to rapid and material loss of market share for SUBOXONE® Film. It is possible that other companies may also subsequently launch generic buprenorphine/naloxone sublingual film products on an "at-risk" basis. Indivior has been preparing for this eventuality and has implemented certain key elements of its contingency plan in light of these expected generic launches (see details on Page 2).

- SUBLOCADE™ net revenues were \$12m, including \$7m in Q4 2018. Key performance indicators (KPIs) continue to improve (see page 4).
- PERSERIS™ was made available in the U.S. in late November 2018. Commercial launch will take place the week of February 18, 2019 with a field force of 50 representatives.
- Reached a definitive agreement (February 4, 2019) to divest rights related to SUBOXONE® Sublingual Tablets (Sai Bo Song™) in the Peoples Republic of China to Zhejiang Pukang Biotechnology Co., Ltd. (Pukang) for total potential consideration of up to \$122.5m based on achieving certain milestones. The agreement is subject to various closing conditions and is anticipated to close in Q4 2019.
- Termination of Arbaclofen Placarbil and ADDEX lead compound due to challenges in their Phase 1 and preclinical studies, respectively, reducing their probability of success below hurdle rates for further investment. This decision does not change our reason to believe in the molecular target (GABAB receptor) and plans are currently being put in place to accelerate our backup program (new lead identification and optimization) in partnership with ADDEX.
- The Group continues in advanced discussions with the U.S. Department of Justice (DOJ) about a possible resolution to its investigations. Please see Notes 8, 9 and 10 beginning on page 22 for further details on provisions and legal proceeding.

Contingency Plan

Indivior has implemented key elements of its contingency plan to help offset the substantial and material near-term impact to net revenue that is expected to result from the “at-risk” launch of generic versions of SUBOXONE® film. The overriding objectives of the contingency plan are to provide for the commercial success of SUBLOCADE™ and PERSERIS™ while ensuring a minimum cash balance of \$250m to remain in compliance with the Group’s debt covenants. Key actions include:

- Reducing outstanding principal on the Term Loan by \$235m in FY 2018 to \$243m;
- Cash conservation measures resulting in FY 2018 ending cash balance of \$924m;
- Initiatives to reduce structural operating expenses, including headcount reductions, R&D reprioritization and other committed savings; and,
- Additionally, Indivior expects to launch an Authorized Generic of SUBOXONE® Film upon confirmation of the launch of generic buprenorphine/naloxone sublingual film products. The launch is expected to capture share of the generic segment and generate an amount of net revenue in the range of tens of U.S.\$ millions.

FY 2019 Guidance

Given uncertainties surrounding how the U.S. market for both SUBOXONE® Film and generic alternatives will ultimately develop, Indivior is unable to provide FY 2019 net revenue and net income guidance at this time.

However, Indivior is providing guidance on the following elements of its business for FY 2019:

- SUBLOCADE net revenue of \$50m to \$70m; and,
- Operating expenses (SG&A and R&D combined) of approximately \$440m to \$460m, excluding exceptional items.

As discussed above, Indivior has executed key elements of its contingency plan. Its overriding objectives are to ensure a minimum cash balance of \$250m to remain in compliance with its debt covenants and to help provide resources to cover the transition period of expected material and rapid loss of SUBOXONE® film net revenue in the U.S. until combined net revenue from SUBLOCADE™ and PERSERIS™, along with continued net revenue from the rest of world (ROW), is able to return the Group to profitable growth.

Indivior intends to provide FY 2019 Group net revenue and net income guidance (before exceptionals and currency) once the total U.S. buprenorphine/naloxone sublingual film market dynamics are clearer, which is anticipated to be at its Q1 2019 results release scheduled for May 2, 2019.

Shaun Thaxter, CEO of Indivior, Commented:

"FY 2018 brought a series of market challenges which resulted in Indivior delivering lower net revenue and only slightly higher adjusted net income compared to the prior year. As we enter FY 2019, we assume we face the imminent "at-risk" launch of generic rivals to SUBOXONE® Film in the U.S. We have prudently prepared for this event, planning and taking the required actions to help ensure we can deliver on our strategic priorities despite the near-term top-line pressures that generic competition to SUBOXONE® Film will bring. Specifically, we have:

- Maintained our focus on cash generation and preserved our balance sheet;
- Continued to assert our IP against the ANDA filers;
- Completed steps that have appropriately adjusted our operating structure;
- Repaid \$235m of outstanding Term Loan balance to lower the outstanding balance to \$243m; and,
- Prepared the launch of an authorized generic of buprenorphine/naloxone sublingual film to participate in the rapidly forming generic market for buprenorphine/naloxone sublingual film.

Together, these actions are designed to help us remain compliant with our borrowing covenants and help the Group to leverage the profitable long-term growth we expect from our new transformational depot technologies.

- In SUBLOCADE™, we are making progress toward a truly new treatment paradigm for OUD patients and the opioid crisis, and the coming year will see us further strengthen our execution in pursuit of our \$1bn-plus net revenue target. With PERSERIS™ we believe we have a differentiated long-acting injectable treatment for schizophrenia, a common co-occurrence of substance use disorders, and the long-sought strategic opportunity we have created to diversify our revenue base. We are confident these products will be the future value drivers of Indivior and our focus in 2019 will be on their successful commercial execution.
- Of course, we could not drive these new launches, together with our base film and tablet business, without our talented and committed global workforce. We are truly grateful that – despite the recent period of disruption and uncertainty – the new organization that has emerged this year is energized and optimistic.
- Finally, in everything we do we think first and foremost about the patient. Our inspiration is to improve the lives of the many patients across all walks of society who suffer from the chronic relapsing conditions of addiction and its co-occurring disorders. This relentless patient-centricity, along with maintaining the highest regulatory and compliance standards, provides the foundational elements of Indivior's long-term success."

FY Operating Review

U.S. Market Update

In 2018, market volume for buprenorphine products continued to grow at low-teen percentage rates, in line with Indivior's expectations. This volume growth was driven by benefits from legislation and regulatory changes that have increased federal and state funding to expand OUD treatment, as well as from broader general awareness of the opioid epidemic.

Indivior supports the swift actions the U.S. government has taken to combat the opioid epidemic, including the recent enactment of the SUPPORT for Patients and Communities Act of 2018, which expands access to buprenorphine medication-assisted treatment (BMAT). These regulatory and legislative initiatives are supporting greater treatment capacity for those in most need and are likely to be manifested in continued growth in lower-priced government channels, such as Medicaid.

As the leader and innovator in the OUD category, Indivior has launched its new monthly buprenorphine depot SUBLOCADE™. The Group is making good progress in the following KPIs that it believes will drive accelerated net revenue growth for SUBLOCADE™ in pursuit of its \$1 billion-plus peak net revenue goal:

SUBLOCADE™ Prescription Journey Timeline KPIs (12/31/18 vs. 9/30/18):

- Formulary Access – reached targeted levels, exiting FY 2018 at 83%.
- The Prescription Journey – reached targeted levels, exiting FY 2018 at 15 to 22 days.
- The Dispensing Yield Rate – increased to 41% from 38%.

SUBLOCADE™ Demand KPIs (12/31/18 vs. 9/30/18):

- HCPs Initiating a Prescription Journey – increased to 2,430 versus 1,870.
- HCPs Administered SUBLOCADE™ – increased to 1,325 versus 824.
- HCPs Administered SUBLOCADE™ to 5-plus patients increased to 232 versus 108.

FY 2018 & Q4 2018 Financial Performance

Total net revenue in FY 2018 decreased 8% to \$1,005m (FY 2017: \$1,093m) at actual exchange rates (-9% at constant exchange rates). In FY 2018, volume improvement from underlying market expansion in the U.S. and net revenue contribution from SUBLOCADE™ (FY 2018: \$12m) were more than offset by the combined impacts of unfavorable mix from the increase in government channels (Medicaid) in the U.S., targeted rebating to maintain formulary access and a decline in SUBOXONE® Film market share. In Q4 2018, total net revenue decreased 11% at actual and 10% at constant exchange rates to \$236m (Q4 2017: \$265m). Along with higher SUBOXONE® Film stocking levels in the U.S. versus Q4 2017, Q4 2018 total net revenue drivers were substantially the same as those for FY 2018. Q4 2018 SUBLOCADE™ net revenue was \$7m.

FY 2018 U.S. net revenue decreased 10% to \$790m (FY 2017: \$877m) and declined 12% in Q4 2018 to \$182m (Q4 2017: \$207m). For both comparative periods, volume benefits from underlying market growth were more than offset by the combined impacts of unfavorable mix from the continued disproportionate growth in government channels (Medicaid), targeted rebating to maintain formulary access and the decline in SUBOXONE® Film market share as a result of competitive pricing pressure from generic buprenorphine/naloxone tablet providers. Improved SUBOXONE® Film pricing was more than offset by tactical rebating activity in connection with formulary access. In Q4 2018, there was higher SUBOXONE® Film stocking levels in the U.S. versus Q4 2017 due to increased anticipation by distributor partners of an “at-risk” generic launch after the CAFC’s decision on November 20, 2018, to vacate the preliminary injunction (PI) previously granted Indivior against DRL. This increase was more than offset by unfavorable mix and higher rebate rates as discussed for the full year.

FY 2018 ROW net revenue decreased 1% at actual exchange rates (3% at constant exchange rates) to \$215m (FY 2017: \$216m). In Q4 2018, ROW net revenue decreased 7% at actual exchange rates (1% at constant exchange rates) to \$54m (Q4 2017: \$58m). For both comparative periods, continued growth in Australasia and Canada were more than offset by impacts in certain European markets from ongoing austerity measures.

FY 2018 gross margin was 87% (FY 2017: 90%) and the gross margin was also 85% in Q4 2018 (Q4 2017: 88%). The decrease in both periods versus the prior year primarily reflects lower net revenue driven by higher rebate rates and unfavorable mix and the impact of contingency planning for an “at-risk” launch of a generic buprenorphine/naloxone sublingual film product.

FY 2018 SG&A expenses as reported were \$494m (FY 2017: \$707m) and \$140m in Q4 2018 (Q4 2017: \$326m). FY 2018 SG&A included net exceptional costs of \$16m. The exceptional costs comprised \$13m related to restructuring and \$40m related primarily to potential redress for ongoing intellectual property related litigation, partially offset by a \$37m gain from the out-licensing of the intranasal naloxone opioid overdose patents. FY 2017 results included exceptional items of \$210m for an increased legal provision related to investigative and antitrust litigation matters and the legal settlement of the Amneal antitrust matter, partially offset by the release of a legacy litigation reserve.

Q4 2018 SG&A included net exceptional costs of \$34m. The exceptional costs comprised \$13m related to restructuring and \$40m related primarily to potential redress for ongoing intellectual property related litigation,

partially offset by an exceptional gain of \$19m related to a further payment for the intranasal naloxone opioid overdose patents as discussed above. Q4 2017 SG&A included total exceptional costs of \$185m for the increased legal provision partially offset by the release of a legacy litigation reserve as described above.

On an adjusted basis, FY 2018 SG&A expenses decreased 4% to \$478m (Adj. FY 2017: \$497m) and in Q4 2018 SG&A expenses decreased by 25% to \$106m (Adj. Q4 2017: \$141m). The decrease in both periods largely reflects benefits from cost savings actions partially offset by the planned investments for launching SUBLOCADE™ and PERSERIS™.

Reported FY 2018 and Q4 2018 R&D expenses were \$91m and \$41m, respectively (FY 2017: \$89m; Q4 2017: \$22m). The increase was primarily driven by the Q4 2018 impairment of the Arbaclofen Placabil and ADDEX lead compounds in development, which have been classified as exceptional items. Excluding exceptionals, FY 2018 and Q4 2018 R&D expenses decreased by 25% to \$67m and by 23% to \$17m, respectively (Adj. FY 2017: \$89m; Adj. Q4 2017: \$22m). The decreases in both periods primarily reflect lower clinical activity and the reprioritization of R&D activities primarily to support SUBLOCADE™ Health Economics and Outcomes Research (HEOR) and post-marketing study commitments.

FY 2018 operating profit was \$292m (FY 2017: \$193m) and Q4 2018 operating profit was \$20m (Q4 2017 operating loss: \$115m). Exceptional costs of \$40m and \$210m are included in the FY 2018 and FY 2017 results, respectively. Exceptional costs of \$58m and \$185m are included in Q4 2018 and Q4 2017, respectively.

On an adjusted basis, FY 2018 operating profit was \$332m (33% margin), an 18% decrease versus \$403m (37% margin) in FY 2017. The decrease reflects lower net revenue, launch investments for SUBLOCADE™ and PERSERIS™, partly offset by a reduction in operating expenses (SG&A and R&D) from cost savings initiatives. On an adjusted basis, Q4 2018 operating profit was \$78m (33% margin), an 11% increase versus \$70m (26% margin) in Q4 2017. The increase reflects benefits from cost savings initiatives that more than offset lower net revenue.

FY 2018 EBITDA (operating profit plus depreciation and amortization) was \$308m (FY 2017: \$206m). Excluding \$40m and \$210m of exceptional items in the current and year-ago results, respectively, FY 2018 adjusted EBITDA was \$348m (Adj. FY 2017: \$416m).

FY 2018 net finance expense was \$14m (FY 2017: \$56m) and nil in Q4 2018 (Q4 2017: \$22m). The reduction in each period reflects lower interest and amortization of financing costs associated with the replacement of the Group's Term Loan borrowing facility in December 2017 and the voluntary repayments of \$235m of the principal balance in the year (\$85m in Q4 2018), and higher interest income.

FY 2018 total tax expense was \$3m, or a rate of 1% (FY 2017 tax charge: \$79m; 58% rate). FY 2018 tax charge included one-time items related to development credits for SUBLOCADE™ of \$34m, including \$1m interest. FY 2017 full-year tax charge also assumed non-deductibility for tax purposes of the exceptional legal provisions and included \$9m related to the release of provisions for unresolved tax matters, partially offset by the impact of the remeasurement of certain deferred tax assets. Excluding exceptional items in FY 2018 pre-tax income and taxation of \$46m (FY 2017: \$91m), the adjusted rate was 15% (Adj. FY 2017: 25%). The decrease in the adjusted rate was due to changes in the geographic mix of earnings, with increased earnings in the UK under the reduced rate for Patent Box, along with a reduction in the U.S. corporate income tax rate from 35% to 21%. Q4 2018 tax credit was \$4m (Q4 2017 charge: \$8m), or a rate of -20% (Q4 2017: 6%). Q4 2018 included a \$10m tax impact on exceptional items and \$5m of exceptional tax items; \$2m relating to finalization of prior year US rate change and \$3m to the finalization of prior year development credits for SUBLOCADE™ (Q4 2017: \$6m release of provisions for unresolved tax matters fully offset by \$6m of taxes on exceptional items). The adjusted tax rate for the quarter was 14% (Q4 2017: 13%).

FY 2018 net income was \$275m (FY 2017: \$58m) as reported. Excluding exceptional costs, FY 2018 net income was broadly unchanged at \$272m (Adj. FY 2017: \$270m). The current and year-ago annual periods include a net

amount of \$3m and \$212m of exceptional items, respectively. In Q4 2018, net income was \$24m (Q4 2017 net loss: \$145m). Excluding exceptional costs, net income for the Q4 was \$67m (Adj. Q4 2017: \$54m). Q4 2018 and Q4 2017 include a net \$43m and \$199m of exceptional items, respectively.

FY 2018 basic EPS was 38 cents (FY 2017: 8 cents) and 37 cents on a diluted basis (FY 2017: 8 cents). On an adjusted basis, excluding the effect of exceptional items, FY 2017 basic EPS was 37 cents (FY 2017: 37 cents) and diluted EPS was 36 cents (FY 2017: 36 cents).

Balance Sheet & Cash Flow

Cash and cash equivalents at the end of FY 2018 were \$924m, an increase of \$61m versus FY 2017 of \$863m. Borrowings, net of issuance costs, were \$241m at the end of the year (FY 2017: \$482m), primarily reflecting the impact of the voluntary repayments of \$235m of outstanding Term Loan principal in H2 2018. As a result, net cash stood at \$681m at year end (FY 2017: \$376), a \$305m improvement in the year.

Net working capital (inventory plus trade and other receivables, less trade and other payables) was negative \$356m at year end, an increase of \$21m from negative \$335m since the end of FY 2017 primarily driven by an increase in sales returns and rebates in the U.S. within payables, partially offset by increased inventories due in part to the launch of SUBLOCADE™.

Cash generated from operations in FY 2018 was \$327m (FY 2017: \$369m), a decrease of \$42m. The reduction in cash generated versus the year-ago period was primarily due to higher operating profit more than offset by a lower increase in legal provisions versus the prior year, net of other working capital changes.

FY 2018 net cash inflow from operating activities was \$303m (FY 2017: \$295m), an increase of \$8m reflecting lower cash from operations more than offset by lower net interest payments of \$8m vs. \$36m in the prior year and reduced tax payments of \$16m vs. \$33m in 2017.

FY 2018 cash outflow from investing activities was \$4m (FY 2017: \$43m), reflecting upfront payments for licensing arrangements with ADDEX and C4X, capitalized development costs, and ongoing investments in facilities, mostly offset by proceeds received from the disposal of the nasal naloxone intangible asset.

FY 2018 cash outflow from financing activities increased to \$237m vs. \$84m in FY 2017, primarily reflecting the impact of the voluntary repayments of \$235m of the outstanding Term Loan balance in H2 2018.

R&D / Pipeline Update

Treatment of Opioid Use Disorder (OUD)

- **SUBLOCADE™ (BUPRENORPHINE EXTENDED-RELEASE INJECTION) FOR SUBCUTANEOUS USE CIII:**
 - SUBLOCADE™ approval in Canada on November 21, 2018.
 - In the US, all Post Marketing Requirement (PMR) and Commitment (PMC) studies are on track.
 - Lifecycle Evidence Generation & Optimization (LEGO) Studies: These studies are dedicated to understand the use of diverted buprenorphine (see our publication list), to demonstrate that craving can be used as an endpoint to predict illicit opioid use, to study the effects of SUBLOCADE™ in the emergency room environment to prevent repeated opioid overdoses and potentially change standards of care, and to investigate how SUBLOCADE™ could potentially block the effects of respiratory depression produced by fentanyl that has been increasingly and directly related to drug overdose deaths in the United States. All studies are on track.
 - RECOVER Study (REmission from Chronic Opioid use: studying enVironmental and socioEconomic factors on Recovery): This is a study collecting up to 24-month longitudinal data encompassing demographics, drug use, drug treatment, family relationships, quality of life, mental and physical health, health-care utilization, crime, housing, employment, and urine drug screening (see our publication list). The 12-month longitudinal analysis top line findings were made available in December 2018; the 24-month last patient out is currently scheduled for March 5, 2019.
 - SUBLOCADE™ ex-US regulatory filings: Filings were made in Australia (May 2018), Israel (July 2018), New Zealand (September 2018) and Europe (November 2018).

- **SUBOXONE® Tablet:**
 - On September 11, 2018, the Chinese National Medical Products Administration (NMPA) approved SUBOXONE® Sublingual Tablets for the treatment of opioid use disorder.
 - Next Steps: (1) *Scheduling*: Chinese government will complete its narcotic scheduling determination for SUBOXONE® Sublingual Tablets. (2) *Import Permit*: Indivior can apply for the import permit or transfer the Import Drug License (IDL) to a qualified third party.
 - On February 4, 2019, announced a definitive agreement to divest the rights related to SUBOXONE® Sublingual Tablets (Sai Bo Song™) in China to Zhejiang Pukang Biotechnology Co., Ltd. (Pukang) for total potential consideration of up to \$122.5m based on achieving certain development and commercial milestones. The agreement is subject to various closing conditions and is anticipated to close in Q4 2019.
- **SUBOXONE® Film:**
 - Israel: Submission on September 3, 2018.
 - Canada: Activities ongoing to supply SUBOXONE® Film to the Canadian Federal Correction Institutions in Q3 2018. Supplemental New Drug Submission (SNDS) anticipated in Q2 2019; Pre-Submission meeting held with Health Canada on October 17, 2018.
 - Europe: Pre-Submission meeting held on October 18, 2018 with BfArM (rapporteur) and HPRA (co-rapporteur); Planned MAA submission in the EU in March 2019.

Treatment of Schizophrenia

- **PERSERIS™ (formerly RBP-7000), Monthly Long-Acting Risperidone Injection:**

- FDA approval on July 27, 2018.
- Initiation of planning and execution of post-marketing and lifecycle management strategies in support of PERSERIS™.

Treatment of Alcohol Use Disorder (AUD)

- **Arbaclofen Placabil (AP):** Although the overall profile of AP was significantly improved as a result of INDIVIOR'S clinical development and reformulation plans, risks related to variability in absorption and enzyme polymorphism still remain and would have to be addressed unequivocally before committing to further development.
- Decision to stop any further development of AP and rather focus on the development of the GABAb positive allosteric modulator family of molecules through our partnership with ADDEX Therapeutics.

Early Stage Asset Development (ESAD)

- **ADX71441 (GABA_B positive allosteric modulator):**
 - Dog EEG study to finalize IND preparation revealed risks narrowing the potential therapeutic window.
 - Decision to stop the development of the lead molecule ADX71441. This decision does not change our reason to believe in the molecular target (GABAb receptor) and plans are currently being put in place to accelerate our backup program (new lead identification & optimization) in partnership with ADDEX Therapeutics.
 - **Continuing partnership** covers \$5.3m National Institute on Drug Abuse (NIDA) grant to support Phase 1 studies upon IND approval.
- **C4X3256 (Selective Orexin 1 (OX1) receptor antagonist):**
 - NIDA grant in the amount of \$500,000 awarded on June 29, 2018 to assess the efficacy of C4X3256 in reducing the positive reinforcing effect of cocaine in rats that exhibit robust, stable levels of cocaine self-administration. Self-administration study started on August 15, 2018.
 - Finalization of all preclinical study reports.
 - Formulation development and stability work to support First Time In Human (FTIH) studies.
 - Finalization of FTIH protocol, Investigators Brochure, Investigational Medicinal Product Dossier.
- **APV202701A (Selective dopamine [DA] D3 receptor antagonist):**
 - Initiation of IND dossier preparation.

Peer-Reviewed Publications

- Ronquest NA, Willson TM, Montejano LB, Nadipelli VR, Wollschlaeger BA (2018) Relationship between buprenorphine adherence and relapse, health care utilization and costs in privately and publicly insured patients with opioid use disorder. *Subst Abuse Rehabil.* 9: 1-20. doi: <https://dx.doi.org/10.2147%2FSAR.S150253>
- Cicero TJ, Ellis MS, Chilcoat HD (2018) Understanding the use of diverted buprenorphine. *Drug and Alcohol Dependence* 193: 117-123. doi: <https://dx.doi.org/10.1016/j.drugalcdep.2018.09.007>
- Heidbreder C (2018) Fighting apathy and lack of awareness in the struggle against substance use disorder. *Nature Reviews Drug Discovery* 17(11): B8-9. <https://biopharmadealmakers.nature.com/pages/npg-latest-edition-bpdm>
- Wang XY, Jiang H, Zhao M, Li J, Gray F, Sheng L, Li Y, Li X, Ling W, Li W, Hao W. Treatment of opioid dependence with buprenorphine/naloxone sublingual tablets: A phase 3 randomized, double-blind, placebo-controlled trial. *Asia-Pacific Psychiatry.* 2018; e12344. <https://doi.org/10.1111/appy.12344>
- Ling W, Nadipelli V, Ronquest N, Albright V, Aldridge A, Learned S, Mehra V, Heidbreder C (2018) Remission from Chronic Opioid Use—Studying Environmental and Socio-economic Factors on Recovery (RECOVER): study design and participant characteristics. *Contemporary Clinical Trials*, 76: 93-103. <https://doi.org/10.1016/j.cct.2018.11.015>
- Haight BR, Learned SM, Laffont CM, Fudala PJ, Zhao Y, Garofalo AS, Greenwald MK, Nadipelli VR, Ling W, Heidbreder C (2018) Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet* (submitted).

Risk Factors

The Board of Directors has carried out a robust assessment to ensure that the Principal Risks, including those that would threaten the Group's business model, future performance, solvency or liquidity are effectively managed and/or mitigated to help ensure the Group remains viable. While the Group aims to identify and manage such risks, no risk management strategy can provide absolute assurance against loss.

Set out below are what the Group considers to be the principal risks that could cause the Group's business model, future performance and solvency or liquidity to differ materially from expected and historical results. Additional risks, not listed here, that the Group cannot presently identify or does not believe to be equally significant, may materially and adversely affect the business, results of operations and financial position. The principal risk factors and uncertainties are not listed in order of significance.

Business operations

- The Group's operations rely on complex processes and systems, strategic partnerships, as well as specially qualified and high performing personnel to develop, manufacture and sell our products. Failure to continuously maintain operational processes and systems as well as to recruit and/or retain qualified personnel could adversely impact products availability and patient health, and ultimately the Group's performance and financials. Additionally, an ever evolving regulatory, political and technological landscape requires that we have the right priorities, capabilities and structures in place to successfully execute on our business strategy and adapt to this changing environment. An example of this evolving landscape is Brexit (decision for the UK to leave the EU), which creates uncertainties and impacts various areas of the Group, including Operations, Regulatory, Supply Chain, and Quality.

Product pipeline, regulatory and safety

- The development and approval of the Group's products is an inherently risky and lengthy process requiring significant financial, research and development resources, and strategic partnerships. Complex regulations with strict and high safety standards govern the development, manufacturing, and distribution of our products. In addition, strong competition exists for strategic collaboration, licensing arrangements, and acquisition targets. Patient safety depends on our ability to perform robust safety assessment and interpretation to ensure that appropriate decisions are made regarding the benefit/risk profiles of our products. Deviations from these quality and safety practices can impact patient safety and market access, which can have a material effect on our Group's performance and prospects.

Commercialization

- Successful commercialization of our products is a critical factor for the Group's sustained growth and robust financial position. Launch of new product involves substantial investment in marketing, market access and sales activities, product stocks, and other investments. If commercialization of a new product is not as successful as anticipated this could have a material impact on the Group's performance and prospects. Generic and brand competition, pricing pressures, private and government reimbursement schemes and systems, negotiations with payors, erosion and/or infringement of

intellectual property (IP) rights, political and socioeconomic factors and HCP/Patient adoption and adherence, if different than anticipated, also can significantly impact the Group's performance and position.

Economic & Financial

- The nature of the pharmaceutical business is inherently risky and uncertain and requires that we make significant financial investments to develop and support the success of our product portfolio. External financing is a key factor in sustaining our financial position and expanding our business growth. Our ability to realize value on those investments is often dependent upon regulatory approvals, market acceptance, strategic partnerships, competition, and legal developments. As a global business, we are also subject to political, economic, and capital markets changes.

Supply Chain

- The manufacturing and supply of our products are highly complex and rely on a combination of internal manufacturing capabilities and third parties for the timely supply of our finished drug and combination drug products. The Group has a single source of supply for buprenorphine, an active product ingredient (API) in the Group's products, and uses contract manufacturing organizations (CMOs) to manufacture, package and distribute our products. The manufacturing of non-sterile pharmaceutical and sterile filled, pharma/combination drug products is subject to stringent global regulatory quality and safety standards, including Good Manufacturing Practice (GMP). Delays or interruptions in our supply chain, and/or product quality failures could significantly disrupt patient access, adversely impact the Group's financial performance; lead to product recalls, and/or potential regulatory actions against the company, along with reputational damages.

Legal & Intellectual Property

- Our pharmaceutical operations, which include controlled substances, are subject to a wide range of laws and regulations from various governmental and non-governmental bodies. Perceived noncompliance with these applicable laws and regulations may result in investigations or proceedings leading the Group to become subject to civil or criminal sanctions and/or pay fines and/or damages, as well as reputational damages.
- Intellectual Property (IP) rights protecting our products may be challenged by external parties, including generic manufacturers. Although we have developed robust patent protection for our products, we are exposed to the risk that courts may decide that our IP rights are invalid and/or that third parties do not infringe our asserted IP rights.
- Unfavorable outcome from government investigations and/or resolutions from legal proceedings, expiry and/or loss of IP rights could have a material adverse impact on the Group's prospects, results of operations and financial condition.
- As previously disclosed in the Prospectus dated November 17, 2014, Indivior has indemnification obligations in favor of Reckitt Benckiser (RB). See further information on legal proceedings in note 10 on pages 23 to 25.

Compliance Product Safety

- Our Group operates on a global basis and the pharmaceutical industry is both highly competitive and regulated. Complying with all applicable laws and regulations, including engaging in commercial activities that are consistent with legal and, industry standards, and our Group's Code of Conduct are core to the Group's mission, culture, and practices. Failure to comply with applicable laws and regulations may subject the Group to civil, criminal and administrative liability, including the imposition of substantial monetary penalties, fines, damages and restructuring the Group's operations through the imposition of compliance or integrity obligations and have a potential adverse impact on the Group's prospects, reputation, results of operations and financial condition.

The Group's annual report for the 2018 financial year will contain additional detail on these principal business risks together with a report on risk appetite.

Exchange Rates

The average and period end exchange rates used for the translation of currencies into US dollars that have most significant impact on the Group's results were:

	FY 2018	FY 2017
GB £ period end	1.2746	1.3513
GB £ average rate	1.3362	1.2881
€ Euro period end	1.1451	1.2001
€ Euro average rate	1.1819	1.1287

[Webcast Details](#)

There will be a presentation at 11:30 GMT (6:30 am Eastern in the USA) hosted by Shaun Thaxter, CEO. This presentation will also be webcast live. The details are below and are available on the Indivior's website at www.indivior.com.

Webcast link: <https://edge.media-server.com/m6/p/at8xatmw>

Confirmation Code:	2271449
Participants, Local - London, United Kingdom:	+44(0)2071 928338
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[For Further Information](#)

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Corporate Website www.indivior.com

This announcement does not constitute an offer to sell, or the solicitation of an offer to subscribe for or otherwise acquire or dispose of shares in the Group to any person in any jurisdiction to whom it is unlawful to make such offer or solicitation.

[Forward-Looking Statements](#)

This announcement contains certain statements that are forward-looking. By their nature, forward-looking statements involve risks and uncertainties as they relate to events or circumstances that may or may not occur in the future. Actual results may differ materially from those expressed or implied in such statements because they relate to future events. Forward-looking statements include, among other things, statements regarding the Indivior Group's financial guidance for 2019 and its medium- and long-term growth outlook, its operational goals, its product development pipeline and statements regarding ongoing litigation and other statements containing the words "subject to", "believe", "anticipate", "plan", "expect", "intend", "estimate", "project", "may", "will", "should", "would", "could", "can", the negatives thereof, variations thereon and similar expressions.

Various factors may cause differences between Indivior's expectations and actual results, including, among others (including those described in the risk factors described in the most recent Indivior PLC Annual Report and in this release): factors affecting sales of Indivior Group's products; the outcome of research and development activities; decisions by regulatory authorities regarding the Indivior Group's drug applications; the speed with which regulatory authorizations, pricing approvals and product launches may be achieved, if at all; the outcome of post-approval clinical trials; competitive developments; difficulties or delays in manufacturing; the impact of existing and future legislation and regulatory provisions on product exclusivity; trends toward managed care and healthcare cost containment; legislation or regulatory action affecting pharmaceutical product pricing, reimbursement or access; claims and concerns that may arise regarding the safety or efficacy of the Indivior Group's products and product candidates; risks related to legal proceedings, including the ongoing investigative and antitrust litigation matters; the Indivior Group's ability to protect its patents and other intellectual property; the outcome of patent infringement litigation relating to Indivior Group's products, including the ongoing ANDA lawsuits; changes in governmental laws and regulations; issues related to the outsourcing of certain operational and staff functions to third parties; uncertainties related to general economic, political, business, industry, regulatory and market conditions; and the impact of acquisitions, divestitures, restructurings, internal reorganizations, product recalls and withdrawals and other unusual items.

Consequently, forward-looking statements speak only as of the date that they are made and should be regarded solely as our current plans, estimates and beliefs. You should not place undue reliance on forward-looking statements. We cannot guarantee future results, events, levels of activity, performance or achievements. Except as required by law, we do not undertake and specifically decline any obligation to update, republish or revise forward-looking statements to reflect future events or circumstances or to reflect the occurrences of unanticipated events.

SUBOXONE® (BUPRENORPHINE AND NALOXONE) SUBLINGUAL FILM (CIII)

Indication

SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII) is a prescription medicine indicated for treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Treatment should be initiated under the direction of healthcare providers qualified under the Drug Addiction Treatment Act.

Important Safety Information

Do not take SUBOXONE® Film if you are allergic to buprenorphine or naloxone as serious negative effects, including anaphylactic shock, have been reported.

SUBOXONE® Film can be abused in a manner similar to other opioids, legal or illicit.

SUBOXONE® Film contains buprenorphine, an opioid that can cause physical dependence with chronic use. Physical dependence is not the same as addiction. Your healthcare provider can tell you more about the difference between physical dependence and drug addiction. Do not stop taking SUBOXONE® Film suddenly without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to this medicine.

SUBOXONE® Film can cause serious life-threatening breathing problems, overdose and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other medications that act on the nervous system (ie, sedatives, tranquilizers, or alcohol). It is extremely dangerous to take nonprescribed benzodiazepines or other medications that act on the nervous system while taking SUBOXONE® Film.

You should not drink alcohol while taking SUBOXONE® Film, as this can lead to loss of consciousness or even death.

Death has been reported in those who are not opioid dependent.

Your healthcare provider may monitor liver function before and during treatment.

SUBOXONE® Film is not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. However, SUBOXONE® Film may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone.

Keep SUBOXONE® Film out of the sight and reach of children. Accidental or deliberate ingestion of SUBOXONE® Film by a child can cause severe breathing problems and death.

Do not take SUBOXONE® Film before the effects of other opioids (eg, heroin, hydrocodone, methadone, morphine, oxycodone) have subsided as you may experience withdrawal symptoms.

Injecting the SUBOXONE® Film product may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems, and cravings.

Before taking SUBOXONE® Film, tell your healthcare provider if you are pregnant or plan to become pregnant. If you are pregnant, tell your healthcare provider as withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary. If you are pregnant or become pregnant while taking SUBOXONE® Film, alert your healthcare provider immediately and you should report it using the contact information provided below.

Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly.

Before taking SUBOXONE® Film, talk to your healthcare provider if you are breastfeeding or plan to breastfeed your baby. The active ingredients of SUBOXONE® Film can pass into your breast milk. You and your healthcare provider should consider the development and health benefits of breastfeeding along with your clinical need for SUBOXONE® Film and should also consider any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how SUBOXONE® Film affects you. Buprenorphine in SUBOXONE® Film can cause drowsiness and slow reaction times during dose-adjustment periods.

Common side effects of SUBOXONE® Film include nausea, vomiting, drug withdrawal syndrome, headache, sweating, numb mouth, constipation, painful tongue, redness of the mouth, intoxication (feeling lightheaded or drunk), disturbance in attention, irregular heartbeat, decrease in sleep, blurred vision, back pain, fainting, dizziness, and sleepiness.

This is not a complete list of potential adverse events associated with SUBOXONE® Film. Please see [full Prescribing Information www.suboxoneREMS.com](http://www.suboxoneREMS.com) for a complete list.

*To report pregnancy or side effects associated with taking SUBOXONE® Film, please call 1-877-782-6966. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

For more information about SUBOXONE® Film, SUBOXONE® (buprenorphine and naloxone) Sublingual Tablets (CIII), or SUBUTEX® (buprenorphine) Sublingual Tablets (CIII), please see the respective [full Prescribing Information](#) and [Medication Guide](#) at www.suboxoneREMS.com.

SUBLOCADE™ (BUPRENORPHINE EXTENDED-RELEASE) INJECTION FOR SUBCUTANEOUS USE (CIII)

INDICATION AND HIGHLIGHTED SAFETY INFORMATION

INDICATION

SUBLOCADE is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.

SUBLOCADE should be used as part of a complete treatment plan that includes counseling and psychosocial support.

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY

- Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously.
- Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements.

HIGHLIGHTED SAFETY INFORMATION

Prescription use of this product is limited under the Drug Addiction Treatment Act.

CONTRAINDICATIONS

SUBLOCADE should not be administered to patients who have been shown to be hypersensitive to buprenorphine or any component of the ATRIGEL® delivery system

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse: SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors.

Respiratory Depression: Life threatening respiratory depression and death have occurred in association with buprenorphine. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBLOCADE.

Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome is an expected and treatable outcome of prolonged use of opioids during pregnancy.

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.

Risk of Opioid Withdrawal With Abrupt Discontinuation: If treatment with SUBLOCADE is discontinued, monitor patients for several months for withdrawal and treat appropriately.

Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to and during treatment.

Risk of Withdrawal in Patients Dependent on Full Agonist Opioids: Verify that patient is clinically stable on transmucosal buprenorphine before injecting SUBLOCADE.

Treatment of Emergent Acute Pain: Treat pain with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect.

ADVERSE REACTIONS

Adverse reactions commonly associated with SUBLOCADE (in ≥5% of subjects) were constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain.

For more information about SUBLOCADE, the full Prescribing Information including BOXED WARNING, and Medication Guide visit www.sublocade.com.

PERSERIS™ (risperidone) for extended-release injectable suspension

INDICATION AND HIGHLIGHTED SAFETY INFORMATION

PERSERIS™ (risperidone) is indicated for the treatment of schizophrenia in adults.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- PERSERIS is not approved for use in patients with dementia-related psychosis.

CONTRAINDICATIONS

PERSERIS should not be administered to patients with known hypersensitivity to risperidone, paliperidone, or other components of PERSERIS.

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: Increased risk of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities. PERSERIS is not approved for use in patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): Manage with immediate discontinuation and close monitoring.

Tardive Dyskinesia: Discontinue treatment if clinically appropriate.

Metabolic Changes: Monitor for hyperglycemia, dyslipidemia and weight gain.

Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in females and males.

Orthostatic Hypotension: Monitor heart rate and blood pressure and warn patients with known cardiovascular disease or cerebrovascular disease, and risk of dehydration or syncope.

Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with a history of a clinically significant low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing PERSERIS if a clinically significant decline in WBC occurs in absence of other causative factors.

Potential for Cognitive and Motor Impairment: Use caution when operating machinery.

Seizures: Use caution in patients with a history of seizures or with conditions that lower the seizure threshold.

ADVERSE REACTIONS

The most common adverse reactions in clinical trials ($\geq 5\%$ and greater than twice placebo) were increased weight, sedation/somnolence and musculoskeletal pain. The most common injection site reactions ($\geq 5\%$) were injection site pain and erythema (reddening of the skin).

For more information about PERSERIS, the full Prescribing Information including BOXED WARNING, and Medication Guide visit www.perseris.com.

Condensed consolidated income statement

		Unaudited Q4 2018 \$m	Unaudited Q4 2017 \$m	Unaudited FY 2018 \$m	Audited FY 2017 \$m
For the three and twelve months ended December 31	Notes				
Net Revenues	2	236	265	1,005	1,093
Cost of Sales		(35)	(32)	(128)	(104)
Gross Profit		201	233	877	989
Selling, general and administrative expenses	3	(140)	(326)	(494)	(707)
Research and development expenses	3	(41)	(22)	(91)	(89)
Operating Profit		20	(115)	292	193
Operating profit before exceptional items		78	70	332	403
Exceptional items	3	(58)	(185)	(40)	(210)
Finance income		6	2	17	7
Finance expense		(6)	(24)	(31)	(63)
Net finance expense before exceptional items		-	(8)	(14)	(42)
Exceptional items		-	(14)	-	(14)
Profit before taxation		20	(137)	278	137
Income tax benefit/(expense)		4	(8)	(3)	(79)
Taxation before exceptional items	5	(11)	(8)	(46)	(91)
Exceptional items within taxation	3,5	15	-	43	12
Net income		24	(145)	275	58
Earnings per ordinary share (cents)					
Basic earnings per share	6	3	(20)	38	8
Diluted earnings per share	6	3	(20)	37	8

Condensed consolidated statement of comprehensive income

		Unaudited Q4 2018 \$m	Unaudited Q4 2017 \$m	Unaudited FY 2018 \$m	Audited FY 2017 \$m
For the three and twelve months ended December 31					
Net income		24	(145)	275	58
Other comprehensive income					
<i>Items that may be reclassified to profit or loss in subsequent years:</i>					
Net exchange adjustments on foreign currency translation		(10)	2	(18)	8
Other comprehensive income/(loss)		(10)	2	(18)	8
Total comprehensive income		14	(143)	257	66

The notes are an integral part of these condensed consolidated financial statements.

Condensed consolidated balance sheet

	Notes	Unaudited Dec 31, 2018 \$m	Audited Dec 31, 2017 \$m
ASSETS			
Non-current assets			
Intangible assets		84	92
Property, plant and equipment		57	54
Deferred tax assets	5	44	58
Other assets		33	15
		218	219
Current assets			
Inventories		78	52
Trade and other receivables		287	278
Current tax receivable		40	32
Cash and cash equivalents		924	863
		1,329	1,225
Total assets		1,547	1,444
LIABILITIES			
Current liabilities			
Borrowings	7	(4)	(5)
Provisions	8	(69)	(143)
Trade and other payables	11	(721)	(665)
Current tax liabilities	5	(24)	(41)
		(818)	(854)
Non-current liabilities			
Borrowings	7	(237)	(477)
Provisions	8	(424)	(316)
Other non-current liabilities		(2)	-
		(663)	(793)
Total liabilities		(1,481)	(1,647)
Net assets/(liabilities)		66	(203)
EQUITY			
Capital and reserves			
Share capital	12	73	72
Share premium		5	2
Other Reserves		(1,295)	(1,295)
Foreign currency translation reserve		(32)	(14)
Retained Earnings		1,315	1,032
Total equity		66	(203)

The notes are an integral part of these condensed consolidated financial statements.

Condensed consolidated statement of changes in equity

	Notes	Share capital	Share Premium	Other reserve	Foreign Currency Translation reserve	Retained earnings	Total equity
		\$m	\$m	\$m	\$m	\$m	\$m
Unaudited							
Balance at January 1, 2018		72	2	(1,295)	(14)	1,032	(203)
Comprehensive income							
Net income		-	-	-	-	275	275
Other comprehensive income		-	-	-	(18)	-	(18)
Total comprehensive income		-	-	-	(18)	275	257
Transactions recognised directly in equity							
Share-based plans		1	3	-	-	15	19
Deferred taxation on share-based plans		-	-	-	-	(7)	(7)
Balance at December 31, 2018		73	5	(1,295)	(32)	1,315	66
Audited							
Balance at January 1, 2017		72	-	(1,295)	(22)	950	(295)
Comprehensive income							
Net income		-	-	-	-	58	58
Other comprehensive income		-	-	-	8	-	8
Total comprehensive income		-	-	-	8	58	66
Transactions recognised directly in equity							
Share-based plans		-	2	-	-	16	18
Deferred taxation on share-based plans		-	-	-	-	8	8
Balance at December 31, 2017		72	2	(1,295)	(14)	1,032	(203)

The notes are an integral part of these condensed consolidated financial statements.

Condensed consolidated cash flow statement

	Unaudited 2018 \$m	Audited 2017 \$m
For the twelve months ended December 31		
CASH FLOWS FROM OPERATING ACTIVITIES		
Operating Profit	292	193
Depreciation, amortization, and impairment	40	13
Gain on disposal of intangible asset	(37)	-
Share-based payments	15	16
Impact from foreign exchange movements	(12)	6
Increase in trade and other receivables	(33)	(59)
Increase in inventories	(31)	(6)
Increase in trade and other payables	58	5
Increase in provisions	35	201
Cash generated from operations	327	369
Interest paid	(25)	(41)
Interest received	17	5
Transaction cost related to loan	-	(5)
Taxes paid	(16)	(33)
Net cash inflow from operating activities	303	295
CASH FLOWS FROM INVESTING ACTIVITIES		
Purchase of property, plant and equipment	(11)	(30)
Purchase of intangible assets	(30)	(13)
Proceeds from license of intangible assets	37	-
Net cash outflow from investing activities	(4)	(43)
CASH FLOWS FROM FINANCING ACTIVITIES		
Proceeds from borrowings	-	487
Repayment of borrowings	(240)	(573)
Proceeds from the issuance of ordinary shares	3	2
Net cash outflow from financing activities	(237)	(84)
Net increase in cash and cash equivalents	62	168
Cash and cash equivalents at beginning of the period	863	692
Exchange differences	(1)	3
Cash and cash equivalents at end of the period	924	863

The notes are an integral part of these condensed consolidated financial statements.

Notes to the condensed consolidated financial statements

1. BASIS OF PREPARATION AND ACCOUNTING POLICIES

Indivior PLC (the 'Company') is a public limited company incorporated and domiciled in the United Kingdom on September 26, 2014. In these condensed consolidated financial statements ('Condensed Financial Statements'), reference to the 'Group' means the Company and all its subsidiaries.

The financial information herein has been prepared in the basis of the accounting policies set out in the annual accounts of the Group for the year ended December 31, 2017 and should be read in conjunction with those annual accounts, except with regards to IFRS 9 and 15 which were implemented in 2018. No standards or interpretations have been adopted before the required implementation date. The Group prepares its annual accounts in accordance with International Financial Reporting Standards (IFRS) and IFRS Interpretations Committee (IFRIC) interpretations as adopted by the European Union and the Companies Act 2006 (the Act) applicable to companies reporting under IFRS. In preparing these condensed consolidated financial statements, the significant judgments made by management in applying the Group's accounting policies and the key sources of estimation uncertainty were the same as those that applied to the consolidated financial statements for the year ended December 31, 2017, with the exception of changes in estimates that are required in determining the provision for income taxes and legal provision.

These consolidated financial statements reflect the Group's adoption of IFRS 15 *Revenue from Contracts with Customers* and IFRS 9 *Financial Instruments* as of January 1, 2018. There were no adjustments made in the current period or prior year comparative as a result of the adoption of these new standards. There will be a more detailed disclosure related to this in the 2018 Annual Report.

The Group adopted IFRS 16 on January 1, 2019. On adoption of IFRS 16, the Group recognized lease liabilities in relation to leases which had previously been classified as 'operating leases' under the principles of IAS 17 Leases. Assets and liabilities arising from a lease are initially measured on a present value basis. Lease liabilities include the net present value of lease payments which are discounted using the group's incremental borrowing rate as of January 1, 2019. The Group applied the modified retrospective approach, which requires the recognition of the cumulative effect of initially applying IFRS 16, as of January 1, 2019, to the retained earnings.

In 2019, the Group will recognize \$29 million of right-of-use assets and \$33 million of lease liabilities and an impact to beginning retained earnings of \$4 million. There will be a more detailed disclosure related to the Group's adoption of IFRS 16 in the 2018 Annual Report.

The condensed consolidated financial statements do not include all the information and disclosures required in the annual financial statements, and should be read in conjunction with the Group's annual financial statements as at December 31, 2017. These condensed consolidated financial statements have been reviewed and not audited. These condensed consolidated financial statements were approved for issue on February 13, 2019.

As disclosed in Note 8, the Group carries a provision of \$438m substantially all relating to the Department of Justice investigations. The final settlement amount may be materially higher than this provision or require payment over a shorter period, which, together with higher than expected loss of revenue following the 'at-risk' launch of generic buprenorphine/naloxone sublingual film products, or the failure for new products to meet revenue growth expectations, could impact the Group's ability to operate. The Directors have taken significant steps to reduce the cost base of the business and manage its capital structure and believe the Group has sufficient liquidity, influence over near-term litigation outcomes and the ability to carry out further measures that may be necessary for the Group to continue as a going concern for at least the next twelve months. However, a combination of the above risks may require additional measures such as further cost savings or a change to the litigation strategy. As such, the above factors indicate the existence of a material uncertainty which may cast significant doubt about the Group's ability to continue as a going concern. The Financial Statements do not include the adjustments that would result if the Group were unable to continue as a going concern. The auditors have indicated that, consistent with the prior year, they expect to include "material uncertainty relating to going concern" and "emphasis of matter in relation to the outcome of litigation" sections within their auditors' report for the 31 December 2018 statutory accounts.

The financial information contained in this document does not constitute statutory accounts as defined in section 434 and 435 of the Act. For the Group's financial statements for the year ended December 31, 2017, the auditors issued (1) an emphasis of matter dealing with the outcome of the Department of Justice and Federal Trade Commission investigations and antitrust litigation details of which are included above and in note 8; and (2) a material uncertainty related to going concern dealing with the existence of a material uncertainty which may cast significant doubt about the Group's ability to continue as a going concern in relation to the Group's involvement in investigations by the Department of Justice and the Federal Trade Commissions as well as antitrust litigation, which would be further adversely impacted should revenues decline and if the uptake of SUBLOCADE™ remains slower than expected. The Group's statutory financial statements for the year ended December 31, 2017 were approved by the Board of Directors on March 6, 2018 and were delivered to the Registrar of Companies.

2. SEGMENT INFORMATION

Operating segments are reported in a manner consistent with the internal reporting provided to the chief operating decision-maker ('CODM'). The CODM, who is responsible for allocating resources and assessing performance of the operating segments, has been identified as the Chief Executive Officer (CEO). The Indivior Group is predominately engaged in a single business activity, which is the development, manufacture and sale of buprenorphine-based prescription drugs for treatment of opioid dependence. The CEO reviews net revenues to third parties, operating expenses by function, and financial results on a consolidated basis for evaluating financial performance and allocating resources. Accordingly, the Group operates in a single reportable segment.

Net revenues

Revenues are attributed to countries based on the country where the sale originates. The following table represents net revenues from continuing operations attributed to countries based on the country where the sale originates and non-current assets, net of accumulated depreciation and amortization, by country. Non-current assets for this purpose consist of property, plant and equipment, intangible assets, and other receivables. Net revenues and non-current assets for the three and twelve months to December 31, 2018 and 2017 were as follows:

Net revenues from sale of goods:

	Q4 2018 \$m	Q4 2017 \$m	FY 2018 \$m	FY 2017 \$m
For the three and twelve months ended December 31				
United States	182	207	790	877
ROW	54	58	215	216
Total	236	265	1,005	1,093

Non-current assets:

	Dec 31, 2018 \$m	Dec 31, 2017 \$m
United States	62	68
ROW	112	93
Total	174	161

3. OPERATING EXPENSES

The table below sets out selected operating expenses information:

	Q4 2018 \$m	Q4 2017 \$m	FY 2018 \$m	FY 2017 \$m
For the three and twelve months ended December 31				
Research and development expenses ¹	(41)	(22)	(91)	(89)
Marketing, selling and general expenses ²	(53)	(51)	(205)	(163)
Administrative expenses ³	(82)	(270)	(271)	(525)
Depreciation and amortization	(4)	(4)	(13)	(13)
Operating lease rentals	(1)	(1)	(5)	(6)
Total	(140)	(326)	(494)	(707)

¹ R&D expenses include \$24m of impairment costs that have been classified as exceptional as outlined in the table below.

² Distribution costs of \$3m previously included in operating expenses have been classified as cost of sales to better reflect the nature of the costs with SUBLOCADE™ launch. The prior year has not been adjusted as the total amount, which was approximately \$3m, is not material.

³ Administrative expenses include exceptional costs in the current and prior year as outlined in table below. Prior year administrative expenses also included non-exceptional expenses of \$36m related to the ongoing protection of the company's intellectual property. These costs were not classified as exceptionals as they primarily related to non-litigation expenses for the ongoing protection of the Group's prospective revenues.

Exceptional Items

	Q4 2018 \$m	Q4 2017 \$m	FY 2018 \$m	FY 2017 \$m
For the three and twelve months ended December 31				
Other operating income ¹	19	-	37	-
Restructuring costs ²	(13)	-	(13)	-
Legal Expenses/Provision ³	(40)	(185)	(40)	(210)
Intangible impairment (R&D) ⁴	(24)	-	(24)	-
Financing costs (debt refinancing) ⁵	-	(14)	-	(14)
Total exceptional items before taxes	(58)	(199)	(40)	(224)
Tax on exceptional items	10	(6)	8	3
Exceptional benefits within tax ⁶	5	6	35	9
Total exceptional items	(43)	(199)	3	(212)

¹ \$37m of exceptional income in FY 2018 (\$19m in Q4) relates to the proceeds received from the out-licensing of nasal naloxone opioid overdose patents which are included within SG&A.

² Restructuring costs relate to the cost savings initiative announced in the HY 2018 results to offset the financial impact of recent adverse U.S. market developments. These consist primarily of redundancy and related costs.

³ \$40m of legal expenses in the current year and quarter relate to potential redress for ongoing intellectual property related litigation with DRL and Rhodes Pharmaceuticals. Exceptional expense of \$185m in Q4 2017 reflects the increased legal provision related to investigative and antitrust litigation matters,

partially offset by the reversal of a legacy litigation reserve. FY 2017 reflects the \$185m and an additional \$25m for the conclusive legal settlement with Amneal Pharmaceuticals LLC relating to anti-trust litigation.

⁴In 2018, Q4 and FY R&D expenses include \$24m of impairment charges related to the Arbaclofen Placabil and lead ADDEX compounds for which development has ceased due to challenges in the Phase 1 and preclinical studies, respectively thereby reduction of their probability of success below hurdle rates for further investment.

⁵Financing costs of \$14m, written off due to the early debt refinancing, were accounted for as a significant modification in accordance with IAS 39 'Financial Instruments: Recognition and Measurement' based on legal release of the debt, the change in currency profile of the overall debt, and the removal and relaxation of financial covenants.

⁶The tax benefit of \$5m for Q4 2018 consists of \$2m relating to finalization of US tax reform change and \$3m to the finalization of prior year development credits for SUBLOCADE™ (Q4 2017: \$6m release of provisions for unresolved tax matters). In FY 2018, there was an exceptional tax credit of \$34m in relation to development credits for SUBLOCADE™ claimed for prior years, rate change impact in the US of \$1m, along with tax on exceptional income and other adjustments of \$8m. Prior year tax exceptionals of \$9m related to the release of provisions for unresolved tax matter partially offset by the impact of the remeasurement of deferred tax asset along with the tax on exceptional income.

4. ADJUSTED RESULTS

The board and management team use adjusted results and measures to give greater insight to the financial results of the Group and the way it is managed. The tables below show the list of adjustments between the reported and adjusted operating profit and net income for both FY/Q4 2018 and FY/Q4 2017.

Reconciliation of operating profit to adjusted operating profit

	Q4 2018 \$m	Q4 2017 \$m	FY 2018 \$m	FY 2017 \$m
For the three and twelve months ended December 31				
Operating profit	20	(115)	292	193
Exceptional selling, general and administrative expenses	34	185	16	210
Exceptional research and development expenses	24	-	24	-
Adjusted operating profit	78	70	332	403

Reconciliation of net income to adjusted net income

	Q4 2018 \$m	Q4 2017 \$m	FY 2018 \$m	FY 2017 \$m
For the three and twelve months ended December 31				
Net Income	24	(145)	275	58
Exceptional selling, general and administrative expenses	34	185	16	210
Exceptional research and development expenses	24	-	24	-
Exceptional financing costs	-	14	-	14
Exceptional tax items	(15)	-	(43)	(12)
Adjusted net income	67	54	272	270

5. TAXATION

The Group calculates tax expense for interim periods using the expected full year rates, considering the pre-tax income and statutory rates for each jurisdiction. The resulting expense is allocated between current and deferred taxes based upon the forecasted full year ratio.

In Q4 2018, the tax expense on adjusted profits amounted to \$11m excluding exceptionals (Q4 2017: \$8m) and represented a quarterly effective tax rate of 14% (Q4 2017: 13% excluding exceptionals). A tax benefit of \$5m was recognized this quarter; \$2m relating to finalization of prior year US rate change and \$3m to the finalization of prior year development credits for SUBLOCADE™ (Q4 2017: \$6m release of provisions for unresolved tax matters). The tax rates as reported for the quarter was -20% (Q4 2017: 6%)

In FY 2018, the tax charge on adjusted profits amounted to \$46m (FY 2017: \$91m) excluding exceptionals and represented a FY tax rate of 15% (FY 2017: 25%, excluding exceptionals).

The decrease in the adjusted effective tax rate to 15% was primarily driven by the relative contribution to pre-tax income by taxing jurisdiction in the quarter, along with the impacts of U.S. Tax Reform rate reduction and UK reduced rate due to patent box benefit. While there may be fluctuations in the rate from quarter to quarter, this rate reduction is expected to be materially sustained in the next year.

In FY 2018, there was an exceptional tax credit of \$34m in relation to development credits for SUBLOCADE™ claimed for prior years, rate change impact in the US of \$2m, along with tax on exceptional income and other adjustments of \$8m. Prior FY tax expense included \$9m of tax relating to a release of provisions for unresolved tax matters, netted by the impact of the re-measurement of deferred tax assets, and are exceptional and \$3m related to the tax effects of the exceptional items within operating profit.

The Group's balance sheet at December 31, 2018 included current tax payables of \$24m (FY 2017: \$41m), current tax receivables of \$40m (FY 2017: \$32m), and deferred tax assets of \$44m (FY 2017: \$58m). The current tax receivable increased due to the booking of the

exceptional tax credit. The deferred tax asset has decreased over prior year balances due to current year activity, largely relating the share award vestings and a decline in share price as at the reporting date.

Other tax matters

The European Commission has announced their intention to open a State Aid investigation into the UK's controlled foreign company ("CFC") financing exemption. At 31 December 2018, the Group has benefited from the UK controlled foreign company financing exemption by approximately \$24 million; however, at present the Group believes no provision is required in respect of this matter.

The United Kingdom ('UK') decision to withdraw from the European Union ('EU') could have a material effect on our taxes. The impact of the withdrawal will not be known until both the EU and the UK develop the exit plan and the related changes in tax laws are enacted. We will adjust our current and deferred income taxes when tax law changes related to the UK withdrawal are substantively enacted and/or when EU law ceases to apply in the UK.

6. EARNINGS PER SHARE

	Q4 2018 cents	Q4 2017 cents	FY 2018 cents	FY 2017 cents
For the three and twelve months ended December 31				
Basic earnings per share	3	(20)	38	8
Diluted earnings per share	3	(20)	37	8
Adjusted basic earnings per share	9	7	37	37
Adjusted diluted earnings per share	9	7	36	36

Basic

Basic earnings per share ("EPS") is calculated by dividing profit for the period attributable to owners of the Company by the weighted average number of ordinary shares in issue during the period.

Diluted

Diluted earnings per share is calculated by adjusting the weighted average number of ordinary shares outstanding to assume conversion of all dilutive potential ordinary shares. The Company has dilutive potential ordinary shares in the form of stock options and awards. The weighted average number of shares is adjusted for the number of shares granted assuming the exercise of stock options.

	2018 thousands	2017 thousands
Weighted average number of shares		
On a basic basis	727,148	721,126
Dilution from share awards and options	23,994	27,356
On a diluted basis	751,142	748,482

Adjusted Earnings

The Directors believe that diluted earnings per share, adjusted for the impact of exceptional items after the appropriate tax amount, provides more meaningful information on underlying trends to shareholders in respect of earnings per ordinary share. A reconciliation of net income to adjusted net income is included in Note 4.

7. FINANCIAL LIABILITIES – BORROWINGS

	Dec 31 2018 \$m	Dec 31 2017 \$m
Current		
Bank loans	(4)	(5)
	(4)	(5)
Non-current		
Bank loans	(237)	(477)
	(237)	(477)
Analysis of net debt		
Cash and cash equivalents	924	863
Borrowings*	(243)	(487)
	681	376

*Borrowings reflects the principal amount drawn before debt issuance costs of \$2m (FY 2017: \$5m).

	Dec 31 2018 \$m	Dec 31 2017 \$m
Reconciliation of net debt		
The movements in the period were as follows:		
Net cash at beginning of period	376	131
Net increase in cash and cash equivalents	61	171
Net repayment of borrowings	240	86
Exchange adjustments	4	(12)
Net cash at end of period	681	376

The net carrying value of current borrowings before issuance costs and cash at bank, as well as trade receivables and trade payables are assumed to approximate their fair values. The terms of the loan in effect at December 31, 2018 are as follows:

	Currency	Nominal interest margin	Maturity	Required annual repayments	Maximum leverage ratio
Term loan facility	USD	Libor (1%) + 4.5%	2022	1%	3.0*

- Nominal interest margin is calculated over three-month LIBOR subject to the LIBOR floor.
- The maximum leverage ratio is a financial covenant to maintain net secured leverage below a specified maximum (*Adjusted aggregated net debt divided by Adjusted EBITDA ratio) which stands at 3.0x.

8. PROVISIONS

	Dec 31 2018 \$m	Dec 31 2017 \$m
Litigation matters	(438)	(438)
Intellectual property related matters	(44)	(19)
Restructuring Program	(8)	-
Other	(3)	(2)
Total	(493)	(459)

The Group is involved in legal and intellectual property disputes as described in Note 10, Legal Proceedings.

The Group carries a provision for investigative and antitrust litigation matters of \$438m. Substantially all of the provision relates to the U.S. Department of Justice investigation. The Group is in advanced discussions with the Department of Justice about a possible resolution to its investigations, although it cannot predict with any certainty whether, when, or at what cost it will reach an ultimate resolution.

In the event the final settlement amount of the DOJ matter is materially higher than the provision or is required to be paid over a shorter period of time, and the Group is further adversely impacted by higher than expected loss of revenue following the 'at-risk' launch of generic buprenorphine/naloxone sublingual film products or the failure for new products to meet revenue growth expectations, the

Group would not continue in business without taking further necessary measures to reduce its cost base and improve its cash flow. The Directors have taken significant steps to reduce the cost base of the business and manage its capital structure. However, a combination of the above risks may require additional measures such as further cost savings or a change to the litigation strategy.

The Group also carries provisions totalling \$44m for intellectual property related matters, \$40m of these relate to potential redress for ongoing intellectual property related litigation with DRL and Rhodes Pharmaceuticals and have been classified as exceptional costs (see note 3).

The final aggregate cost of these matters may be materially higher than the amount provided.

The Group believes that it has strong defences in the antitrust and other litigations and is actively litigating these matters. Indivior cannot predict with any certainty whether, when, or at what cost it will reach ultimate resolution of the antitrust and other litigation matters.

9. CONTINGENT LIABILITIES

Other than the disputes for which provisions have been taken as disclosed in Note 8, 'Provisions' or as separately disclosed in Note 5, 'Taxation', reliable estimates could not be made of the potential range of cost required to settle legal or intellectual property disputes where the possibility of losses is more than remote. Descriptions of the significant tax, legal and other disputes to which the Group is a party are set out in Note 5, 'Taxation' and Note 10, 'Legal Proceedings.'

10. LEGAL PROCEEDINGS

Litigation Matters

Department of Justice Investigation

- A U.S. federal criminal grand jury investigation of Indivior initiated in December 2013 is continuing, and includes marketing and promotion practices, pediatric safety claims, and overprescribing of medication by certain physicians. The U.S. Attorney's Office for the Western District of Virginia has served a number of subpoenas relating to SUBOXONE® Film, SUBOXONE® Tablet, SUBUTEX® Tablet, buprenorphine and our competitors, among other issues. The Group has responded to the subpoenas and has otherwise cooperated fully with the Department and prosecutors and will continue to do so. The Group is in advanced discussions with the Department of Justice about a possible resolution to its investigation. However, it is not possible to predict with any certainty the potential impact of this investigation on the Group or to quantify the ultimate cost of a resolution.

State Subpoenas

- On October 12, 2016, Indivior was served with a subpoena for records from the State of Connecticut Office of the Attorney General under its Connecticut civil false claims act authority. The subpoena requests documents related to the Group's marketing and promotion of SUBOXONE® products and its interactions with a non-profit third-party organization. On November 16, 2016, Indivior was served with a subpoena for records from the State of California Department of Insurance under its civil California insurance code authority. The subpoena requests documents related to SUBOXONE® Film, SUBOXONE® Tablet, and SUBUTEX® Tablet. The State has served additional deposition subpoenas on Indivior in 2017 and served a subpoena in 2018 requesting documents relating to the bioavailability / bioequivalency of SUBOXONE® Film, manufacturing records for the product and its components, and the potential to develop dependency on SUBOXONE Film. The Group is fully cooperating in these civil investigations.

FTC investigation and Antitrust Litigation

- The U.S. Federal Trade Commission's investigation remains pending. Litigation regarding privilege claims has now been resolved. Indivior has produced certain documents that it had previously withheld as privileged; other such documents have not been produced.
- Civil antitrust claims have been filed by (a) a putative class of direct purchasers, (b) a putative class of end payor purchasers, (c) Amneal Pharmaceuticals LLC (Amneal), a manufacturer of generic buprenorphine / naloxone tablets, and (d) a group of states, now numbering 41, and the District of Columbia. Each set of plaintiffs filed generally similar claims alleging, among other things, that Indivior violated U.S. federal and/or state antitrust and consumer protection laws in attempting to delay generic entry of alternatives to SUBOXONE® tablets. Plaintiffs further allege that Indivior unlawfully acted to lower the market share of these products. The Group has settled the dispute with Amneal, and Amneal has dismissed its claims against the Group with prejudice. The other antitrust cases are pending in federal court in the Eastern District of Pennsylvania. Pre-trial proceedings were coordinated. The fact discovery period has closed; expert discovery and briefing on class certification issues is ongoing. This States' lawsuit relates to the antitrust investigation conducted by various states, as discussed in previous filings.

Estate of John Bradley Allen

- On December 27th, 2016, the Estate of John Bradley Allen filed a civil complaint against Indivior, among other parties, in the Northern District of New York seeking relief under Connecticut's products liability and unfair trade practices statutes for damages allegedly caused by SUBOXONE®. This lawsuit was dismissed without prejudice on August 9, 2018.

Opioid Class Action Litigation.

- In February 2019, Indivior PLC, along with other manufacturers of opioid products, was named in the national civil opioid class action litigation brought by state and local governments, alleging misleading marketing messages. This complaint was filed by several Kentucky public health agencies in the class action consolidated in the federal district court for the Northern District of Ohio. Indivior has not been served with the complaint, but these claims present the potential that the company could be found liable for civil damages in this and other civil opioid class actions.

Intellectual property related matters

ANDA Litigation

- Actavis is currently enjoined from launching a generic buprenorphine/naloxone film product until April 2024 based on a June 3, 2016 ruling by the United States District Court for the District of Delaware finding the asserted claims of the '514 Patent valid and infringed. Actavis has appealed this ruling. On October 24, 2017, Actavis received tentative approval from FDA for at least its 8mg/2mg generic product under its Abbreviated New Drug Application (ANDA) No. 204383 and on November 15, 2017, it received tentative approval for its 12mg/3mg generic product under ANDA No. 207087. Litigation against Actavis is also pending in the District of Delaware on Indivior's more recently listed Orange Book Patents: U.S. Patent Nos. 9,687,454 (the '454 Patent), and 9,931,305 (the '305 Patent).
- On August 31, 2017, the United States District Court for the District of Delaware found that asserted claims of U.S. Patent No. 8,017,150 (the '150 Patent), U.S. Patent No. 8,900,497 (the '497 Patent), and the '514 Patent are valid but not infringed DRL. Indivior has appealed this ruling. Litigation against DRL is currently pending in the District of New Jersey on the '454 and '305 patents. DRL received final FDA approval for all four strengths of its generic buprenorphine/naloxone film product on June 14, 2018, and immediately launched its generic buprenorphine/naloxone film product "at-risk." On June 15, 2018, Indivior filed a motion with the United States District Court for the District of New Jersey seeking a Temporary Restraining Order (TRO) and Preliminary Injunction (PI) pending the outcome of a trial on the merits of the '305 Patent. The court granted Indivior a two-week TRO, preventing DRL from continuing to sell or offer to sell its generic product. Indivior was required to post an \$18 million surety bond to cover DRL's damages in the event of an Indivior loss of its patent case against DRL. On June 28, 2018, the court heard oral argument in support of Indivior's motion for a PI against DRL and, at the conclusion of this hearing, extended the TRO for an additional 14 days in order to rule on the PI motion and required Indivior to post another \$18 million surety bond. On July 13, 2018, the District Court issued its ruling granting Indivior a PI against DRL. On July 18, 2018, the District Court ordered Indivior to post a surety bond for \$72 million (that total figure being inclusive of the \$36 million surety bond already posted) in connection with the PI. DRL appealed to the United States Court of Appeals for the Federal Circuit (CAFC) on the same day. On November 20, 2018, the CAFC issued a decision vacating the PI against DRL. Indivior filed a timely petition for rehearing and rehearing en banc on December 20, 2018. The CAFC denied the petition on February 4, 2019. On February 5, 2019, Indivior filed an emergency motion to stay the issuance of mandate pending the resolution of the appeal of the District of Delaware decision with respect to the '514 patent, and pending Indivior's forthcoming petition for a writ of certiorari to the Supreme Court of the United States in the PI matter. The CAFC denied that motion on February 11, 2019, and Indivior filed a second emergency motion to stay the mandate pending resolution of its forthcoming application for an administrative stay to the Supreme Court of the United States. The CAFC denied that motion and ordered issuance of the mandate on February 19, 2019. Indivior will file an application to the Supreme Court of the United States requesting a stay of the mandate pending resolution of its forthcoming petition for *certiorari* seeking to overturn the CAFC's PI vacatur. Any DRL generic product sales in the U.S. would be on an "at-risk" basis, subject to the outcome of the appeal of the non-infringement judgment related to U.S. Patent Nos. 8,603,514, as well as the ongoing litigation against DRL in the District of New Jersey. On February 12, 2019, the CAFC granted Indivior's request to expedite the appeal of the non-infringement judgment in the '514 patent case to the extent it will be placed on the next available oral argument calendar.
- On November 13, 2018, DRL filed two separate petitions for *inter partes* review of the '454 Patent with the USPTO. Indivior's preliminary responses are due March 6, 2019 and March 7, 2019.
- Teva filed a 505(b)(2) New Drug Application (NDA) for a 16mg/4mg strength of buprenorphine/naloxone film (CASSIPA™). Indivior, Aquestive Pharmaceuticals (formerly known as MonoSol Rx) and Teva agreed that infringement by Teva's 16mg/4mg dosage strength would be governed by the infringement ruling as to Dr. Reddy's 8mg/2mg dosage strength that was the subject of the trial in November 2016. Accordingly, the non-infringement ruling in the Dr. Reddy's case means that the Teva 16mg/4mg dosage strength has been found not to infringe. Indivior has appealed this November 2016 ruling. Litigation is ongoing against Teva in the District of New Jersey on the '454 patent and '305 patent. Teva received final approval from the FDA for CASSIPA on September 7, 2018 and has agreed to be bound by the decision in the DRL PI case. Teva is therefore enjoined from launching CASSIPA unless and until the CAFC issues a mandate vacating the PI against DRL. Any sales of CASSIPA in the U.S. would be on an "at-risk" basis, subject to the outcome of the appeal of the non-infringement judgment related to the '514 patent, as well as the ongoing litigation against Teva and DRL in the District of New Jersey.
- Trial against Alvogen in the lawsuit involving the '514 and '497 Patents for SUBOXONE® Film took place in September 2017. The trial was limited to the issue of infringement because Alvogen did not challenge the validity of either patent. On March 22, 2018, the

United States District Court for the District of Delaware issued its ruling finding both patents not infringed by Alvogen. Indivior has appealed this ruling. Litigation against Alvogen is also pending in the United States District Court for the District of New Jersey on the '454 Patent and the '305 Patent. On January 22, 2019, Indivior filed a motion for a temporary restraining order ("TRO") and preliminary injunction in the District of New Jersey, requesting that the Court restrain the launch of Alvogen's generic buprenorphine/naloxone film product until a trial on the merits of the '305 patent. Alvogen received approval for its generic product on January 24, 2019. The same day, the District of New Jersey granted a TRO until February 7, 2019, with a PI hearing scheduled for that day. On January 31, 2019, Indivior and Alvogen entered in to an agreement whereby Alvogen is enjoined from the use, offer to sell, or sale within the United States, or importation into the United States, of its generic buprenorphine and naloxone sublingual film product unless and until the CAFC issues a mandate vacating the PI against DRL. Any Alvogen generic product sales in the U.S. would be on an "at-risk" basis, subject to the outcome of the appeal of the non-infringement judgment related the '514 patent, as well as the ongoing litigation against Alvogen in the District of New Jersey. On February 12, 2019, the CAFC granted Indivior's request to expedite the appeal of the non-infringement judgment in the '514 patent case to the extent it will be placed on the next available oral argument calendar.

- By a Court order dated August 22, 2016, Indivior's SUBOXONE® Film patent litigation against Sandoz was dismissed without prejudice because Sandoz is no longer pursuing Paragraph IV certifications for its proposed generic formulations of SUBOXONE® Film.
- On September 25, 2017, Indivior settled its SUBOXONE® Film patent litigation against Mylan, the terms of which are confidential. Mylan received final FDA approval for its generic version of the 8mg buprenorphine/naloxone film product on June 14, 2018.
- On May 11, 2018, Indivior settled its SUBOXONE® Film patent litigation against Par. Under the terms of the settlement agreement, Par can launch its generic buprenorphine/naloxone film product on January 1, 2023, or earlier under certain circumstances. Other terms of the settlement agreement are confidential. So far as Indivior is aware, FDA to date has not granted tentative or final approval for Par's generic buprenorphine/naloxone film product.

Rhodes Pharmaceuticals

- On December 23, 2016 Rhodes Pharmaceuticals filed a complaint against Indivior in the United States District Court for the District of Delaware, alleging that Indivior's sale of SUBOXONE® Film in the U.S. infringes one or more claims of U.S. Patent No. 9,370,512 (the '512 Patent). The asserted patent, which was issued in June 2016, claims priority to an application filed in August 2007.
- On March 16, 2018, Indivior filed a petition for inter partes review (IPR) with the United States Patent and Trademark Office (USPTO) asserting that all claims of the '512 Patent are invalid.
- On October 4, 2018, the USPTO declined to institute an IPR on the challenged claims of the '512 patent.

11. TRADE AND OTHER PAYABLES

	Dec 31 2018 \$m	Dec 31 2017 \$m
Sales returns and rebates	(510)	(433)
Trade payables	(47)	(40)
Accruals	(149)	(179)
Other tax and social security payables	(15)	(13)
Total	(721)	(665)

Sales return and rebate accruals, primarily in the U.S., are provided in respect of the estimated rebates, discounts or allowances payable to direct and indirect customers. Accruals are made at the time of sale while the actual amounts to be paid are based on claims made some time after the initial recognition of the sale. The estimated amounts may not reflect the final outcome and are subject to change dependent upon, amongst other things, the payor channel (e.g. Medicaid, Medicare, Managed Care, etc.) and product mix. Accrual balances are reviewed and adjusted quarterly in the light of actual experience of rebates, discounts or allowances given and returns made and any changes in arrangements. Future events may cause the assumptions on which the accruals are based to change, which could affect the future results of the Group.

12. SHARE CAPITAL

	Equity Ordinary Shares	Issue price	Nominal value \$m
Issued and fully paid			
At January 1, 2018	721,462,733	\$0.10	72
Allotments	6,978,920	\$0.10	1
At December 31, 2018	728,441,653		73

	Equity Ordinary Shares	Issue price	Nominal value \$m
Issued and fully paid			
At January 1, 2017	720,597,566	\$0.10	72
Allotments	865,167	\$0.10	-
At December 31, 2017	721,462,733		72

Allotment of ordinary shares

During the period, 6,978,920 ordinary shares (2017: 865,167) were allotted to satisfy vestings/exercises under the Group's Long-Term Incentive Plan and U.S. Employee Stock Purchase Plan.

13. POST BALANCE SHEET EVENTS

On February 4, 2019, the Court of Appeals for the Federal Circuit (CAFC) denied Indivior's motion for rehearing and rehearing *en banc* following the CAFC's ruling vacating the preliminary injunction (PI) granted against Dr. Reddy's Laboratories (DRL). The CAFC has also denied Indivior's requests to stay issuance of the mandate pending the outcomes of the '514 Patent appeal currently pending with the CAFC and its forthcoming petition for *certiorari* with the Supreme Court. The CAFC has ordered issuance of the mandate on February 19, 2019. Indivior will file an application to the Supreme Court of the United States requesting a stay of the mandate pending resolution of its forthcoming petition for *certiorari* seeking to overturn the CAFC's PI vacatur. If the mandate issues, DRL will no longer be prevented from selling, offering to sell, or importing its generic buprenorphine/naloxone sublingual film product in the U.S. We assume that DRL will resume the "at-risk" launch of its generic film product in the U.S. following the issuance of the mandate. Further, pursuant to an agreement reached with Alvogen, we assume that they will also launch their generic product in the U.S. "at-risk" once the mandate issues and DRL is permitted to launch.

Indivior reached a definitive agreement (February 4, 2019) to divest rights related to SUBOXONE® Sublingual Tablets (Sai Bo Song™) in the Peoples Republic of China to Zhejiang Pukang Biotechnology Co., Ltd. (Pukang) for total potential consideration of up to \$122.5m based on achieving certain milestones. The agreement is subject to various closing conditions and is anticipated to close in Q4 2019.

In the Half Year 2018 results, the Group announced its intention to implement a program to streamline the Group and reduce certain costs. This resulted in a further reduction in headcount of over 120 employees in Q1 2019. Incremental costs to affect the savings will be reflected as an exceptional cost in Q1 2019.

EXHIBIT 10

Indivior Provides Legal and Trading Update; Confirms Launch of PERSERIS™ and Key Elements of Contingency Plan

Slough, UK, 18 December 2018 – Indivior PLC (the “Company”) with today’s announcement and accompanying supplement published on its website (<http://www.indivior.com>) is:

- Providing an update on legal matters relating to the Court of Appeals for the Federal Circuit (CAFC) vacating the preliminary injunction (PI) against Dr. Reddy’s Laboratories (DRL), including next steps and estimated timelines;
- Confirming that the Company expects to meet its overall FY 2018 net revenue and net income guidance, including exceeding FY 2018 SUBLOCADE™ net revenue guidance;
- Providing an update on SUBLOCADE™ KPIs;
- Confirming the launch of PERSERIS™; and,
- Confirming key elements of its contingency plan, should a generic buprenorphine/naloxone sublingual film product enter the U.S. market.

This announcement and the accompanying supplement substitutes for the Capital Markets Day that was originally scheduled for December 5th and will now be postponed until after the Company’s FY 2018 financial results on February 14th, 2019. A date will be confirmed later.

CAFC / DRL Update:

On November 20th, the CAFC vacated the preliminary injunction (PI) granted by the U.S. District Court of New Jersey, which enjoined DRL from entering the U.S. market. However, the exact timing for DRL’s potential “at-risk” market re-entry in the U.S. is unknown, as the PI remains in effect until the issuance of a mandate by the CAFC. The “mandate” is a formal filing by the CAFC that returns the case to the District Court for actions consistent with the CAFC’s ruling.

On December 11th, the CAFC denied DRL’s motion (filed on November 20th) to issue the mandate immediately or, alternatively, stay the PI pending issuance of the mandate. Consequently, the PI will remain in place and DRL will remain enjoined from resuming the “at-risk” launch in the U.S. market of its generic buprenorphine/naloxone sublingual film until after the mandate issues. Indivior will file a petition for a rehearing by the original panel of judges as well as a rehearing *en banc* by December 20th. The CAFC must rule on Indivior’s petition for the rehearings before the mandate can be issued.

Even if the CAFC issues the mandate and the PI is vacated, any DRL generic product sales in the U.S. would be on an “at-risk” basis, subject to the outcome of the appeal of the non-infringement judgments related to U.S. Patent Nos. 8,603,514 and 8,017,150 – as well as ongoing litigation against DRL in the District of New Jersey asserting recently-granted Orange Book-listed patents (U.S. Patent Nos. 9,931,305 and 9,687,454).

Indivior has made it clear that it intends to continue its vigorous assertion and protection of its intellectual property with respect to SUBOXONE® Film and will seek redress and damages from any “at-risk” launch following success in any of these cases.

Trading Update & Financial Guidance for FY 2018:

Assuming no generic buprenorphine/naloxone sublingual film entry in the U.S. before the beginning of FY 2019, Indivior confirms that it expects to meet its FY 2018 financial guidance of net revenue of \$990 to \$1,020 million and net income of \$230 to \$255 million.

Indivior also confirms that SUBLOCADE™ net revenues for FY 2018 will exceed the top end of its previous guidance range of \$8 to \$10 million by approximately \$2 million.

The Company expects to give financial guidance for FY 2019 with its FY 2018 results on February 14th, 2019, when the Company anticipates having greater clarity on U.S. market conditions.

SUBLOCADE™ KPIs Update:

Prescription Journey KPIs have reached or are progressing toward their target range:

- As of 11/30/18 formulary access stood at 83% (versus 82% at 9/30/18).
- As of 10/31/18 (latest available data) the Prescription Journey timeline of 16 to 23 days was generally in the Company's target range (versus 16 to 22 days at 9/30/18).
- As of 10/31/18 (latest available data) the Dispense Conversion Rate improved modestly to 37% (versus 36% at 9/30/18) and continues towards the Company's target of 50%.

HCP trial and adoption KPIs as of November 30th, 2018:

- HCPs Initiating a Prescription Journey increased to 2,270 (versus 1,870 at 9/30/18).
- HCPs Administered SUBLOCADE™ increased to 1,195 (versus 824 at 9/30/18).
- HCPs Administered SUBLOCADE™ to 5-plus patients increased to 199 (versus 108 at 9/30/18).

Indivior remains confident in its peak net revenue goal for SUBLOCADE™ of \$1 billion-plus.

PERSERIS™ Update:

Indivior is confirming today that the Company is moving ahead with the launch of PERSERIS™ in the U.S. with a sales force consisting of approximately 50 representatives. While PERSERIS™ has been available in the U.S. since November 19th, the commercial launch is scheduled to take place in February 2019. The PERSERIS™ team is currently engaged in creating payor access, growing prescriber awareness and interest, as well as establishing its INSUPPORT™ patient hub.

Indivior remains confident in its peak net revenue goal for PERSERIS™ of \$200 to \$300 million.

Contingency Planning:

Indivior has updated its contingency plan to reflect current market conditions and future outlook. The key event which may adversely impact consolidated near-term net revenue and cash flow is the potential launch of generic buprenorphine/naloxone film in the U.S. market. Until the timing of potential generic film entry is certain, the full financial impact cannot be assessed.

The objective of the contingency plan is to provide for the commercial success of SUBLOCADE™ and PERSERIS™ while ensuring a minimum cash balance of \$250 million to remain in compliance with the Company's debt covenants. At the end of November 2018, the Company had a cash balance of approximately \$910 million.

The contingency plan is expected to cover the transition period of net revenue loss due to potential generic erosion of the Company's SUBOXONE® Film franchise until combined net revenue growth from SUBLOCADE™ and PERSERIS™ gathers sufficient momentum to return the Company to profitable growth.

Indivior's actions to meet the Company's objective of maintaining a \$250 million minimum cash balance include:

- Launching an Authorized Generic of SUBOXONE® Film upon entry by a generic buprenorphine/naloxone film by an ANDA competitor. The launch is expected to capture some share of the generic segment and generate a small amount of net revenue in the range of tens of \$ millions;
- Optimizing the profitability of the base U.S. and Rest of World businesses; and,
- Streamlining actions to materially reduce Indivior's cost base to a level appropriate to the expected level of net revenue in such changed U.S. market conditions, the detail of which will depend on the exact timing of any generic entry. These savings would be derived primarily from SG&A and R&D, and would be incremental to the previously-announced targeted annual savings of \$135 to \$155 million versus the Company's planned operating and R&D expense base for FY 2018.

Summary:

"As the leading provider of buprenorphine-based medication-assisted treatment for opioid dependence, Indivior has a responsibility to sustain our work on behalf of patients suffering from this condition" said Shaun Thaxter, CEO of Indivior. "With SUBLOCADE™ we believe we have a potentially transformational treatment for opioid dependence. The setbacks we have experienced this year will not impede our relentless search for better treatment outcomes for patients and better options for healthcare professionals. However, given the potential for a dramatically altered market, we are prepared to take the difficult but necessary steps to ensure the viability of the business and, above all else, our ability to deliver the potential of SUBLOCADE™ through a period of challenge.

"We also remain excited about the potential of PERSERIS™ and currently are looking forward to commercial launch in February 2019. This differentiated treatment for schizophrenia provides us another attractive growth avenue in a complex disease space that often is a co-occurring disorder of substance use disorders. We look forward to sharing more of our go-to-market plans and performance updates for both SUBLOCADE™ and PERSERIS™ at our Capital Markets Day next year."

Details of the December 18th call are as follows:

Timing: 13:00 London Time / 8:00 a.m. New York Time

Webcast link: <https://edge.media-server.com/m6/p/n2jx9z2b>

Confirmation Code:

3538598

Participants, Local - London, United Kingdom:

+44 (0) 330 336 9125

Participants, Local - New York, United States of America:

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For Further Information

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About Indivior

Indivior is a global specialty pharmaceutical company with a 20-year legacy of leadership in patient advocacy and health policy while providing education on evidence-based treatment models that have revolutionized modern addiction treatment. The name is the fusion of the words individual and endeavor, and the tagline “Focus on you” makes the Company’s commitment clear. Indivior is dedicated to transforming addiction from a global human crisis to a recognized and treated chronic disease. Building on its global portfolio of opioid dependence treatments, Indivior has a strong pipeline of product candidates designed to both expand on its heritage in this category and address other chronic conditions and co-occurring disorders of addiction, including alcohol use disorder and schizophrenia. Headquartered in the United States in Richmond, VA, Indivior employs more than 900 individuals globally and its portfolio of products is available in over 40 countries worldwide. Visit www.indivior.com to learn more.

Forward-Looking Statements

This announcement contains certain statements that are forward-looking and which should be considered, amongst other statutory provisions, in light of the safe harbor provisions of the United States Private Securities Litigation Reform Act of 1995. By their nature, forward-looking statements involve risk and uncertainty as they relate to events or circumstances that may or may not occur in the future. Actual results may differ materially from those expressed or implied in such statements because they relate to future events. Forward-looking statements include, among other things, statements regarding the Indivior Group’s financial guidance for 2018 and its medium- and long-term growth outlook, its operational goals, its product development pipeline and statements regarding ongoing litigation.

Various factors may cause differences between Indivior's expectations and actual results, including: factors affecting sales of Indivior Group’s products; the outcome of research and development activities; decisions by regulatory authorities regarding the Indivior Group’s drug applications; the speed with which regulatory authorizations, pricing approvals and product launches may be achieved; the outcome of post-approval clinical trials; competitive developments; difficulties or delays in manufacturing; the impact of existing and future legislation and regulatory provisions on product exclusivity; trends toward managed care and healthcare cost containment; legislation or regulatory action affecting pharmaceutical product pricing, reimbursement or access; claims and concerns that may arise regarding the safety or efficacy of the Indivior Group’s products and product candidates; risks related to legal proceedings, including the ongoing investigative and antitrust litigation matters; the Indivior Group’s ability to protect its patents and other intellectual property; the outcome of patent infringement litigation relating to Indivior Group’s products, including the ongoing ANDA lawsuits; changes in governmental laws and regulations; issues related to the outsourcing of certain operational and staff functions to third parties; uncertainties related to general economic, political, business, industry, regulatory and market conditions; and the impact of acquisitions, divestitures, restructurings, internal reorganizations, product recalls and withdrawals and other unusual items.

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About SUBOXONE®

Indication

SUBOXONE® (buprenorphine and naloxone) Sublingual Film (CIII) is a prescription medicine indicated for treatment of opioid dependence and should be used as part of a complete treatment plan to include counseling and psychosocial support.

Treatment should be initiated under the direction of healthcare providers qualified under the Drug Addiction Treatment Act.

Important Safety Information

Do not take SUBOXONE® Film if you are allergic to buprenorphine or naloxone as serious negative effects, including anaphylactic shock, have been reported.

SUBOXONE® Film can be abused in a manner similar to other opioids, legal or illicit.

SUBOXONE® Film contains buprenorphine, an opioid that can cause physical dependence with chronic use. Physical dependence is not the same as addiction. Your healthcare provider can tell you more about the difference between physical dependence and drug addiction. Do not stop taking SUBOXONE® Film suddenly without talking to your healthcare provider. You could become sick with uncomfortable withdrawal symptoms because your body has become used to this medicine.

SUBOXONE® Film can cause serious life-threatening breathing problems, overdose and death, particularly when taken by the intravenous (IV) route in combination with benzodiazepines or other medications that act on the nervous system (ie, sedatives, tranquilizers, or alcohol). It is extremely dangerous to take nonprescribed benzodiazepines or other medications that act on the nervous system while taking SUBOXONE® Film.

You should not drink alcohol while taking SUBOXONE® Film, as this can lead to loss of consciousness or even death.

Death has been reported in those who are not opioid dependent.

Your healthcare provider may monitor liver function before and during treatment.

SUBOXONE® Film is not recommended in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment. However, SUBOXONE® Film may be used with caution for maintenance treatment in patients with moderate hepatic impairment who have initiated treatment on a buprenorphine product without naloxone.

Keep SUBOXONE® Film out of the sight and reach of children. Accidental or deliberate ingestion of SUBOXONE® Film by a child can cause severe breathing problems and death.

Do not take SUBOXONE® Film before the effects of other opioids (eg, heroin, hydrocodone, methadone, morphine, oxycodone) have subsided as you may experience withdrawal symptoms.

Injecting the SUBOXONE® Film product may cause serious withdrawal symptoms such as pain, cramps, vomiting, diarrhea, anxiety, sleep problems, and cravings.

Before taking SUBOXONE® Film, tell your healthcare provider if you are pregnant or plan to become pregnant. If you are pregnant, tell your healthcare provider as withdrawal signs and symptoms should be monitored closely and the dose adjusted as necessary. If you are pregnant or become pregnant while taking SUBOXONE® Film, alert your healthcare provider immediately and you should report it using the contact information provided below.

Opioid-dependent women on buprenorphine maintenance therapy may require additional analgesia during labor.

Neonatal opioid withdrawal syndrome (NOWS) is an expected and treatable outcome of prolonged use of opioids during pregnancy, whether that use is medically-authorized or illicit. Unlike opioid withdrawal syndrome in adults, NOWS may be life-threatening if not recognized and treated in the neonate. Healthcare professionals should observe newborns for signs of NOWS and manage accordingly.

Before taking SUBOXONE® Film, talk to your healthcare provider if you are breastfeeding or plan to breastfeed your baby. The active ingredients of SUBOXONE® Film can pass into your breast milk. You and your healthcare provider should consider the development and health benefits of breastfeeding along with your clinical need for SUBOXONE® Film and should also consider any potential adverse effects on the breastfed child from the drug or from the underlying maternal condition.

Do not drive, operate heavy machinery, or perform any other dangerous activities until you know how SUBOXONE® Film affects you. Buprenorphine in SUBOXONE® Film can cause drowsiness and slow reaction times during dose-adjustment periods.

Common side effects of SUBOXONE® Film include nausea, vomiting, drug withdrawal syndrome, headache, sweating, numb mouth, constipation, painful tongue, redness of the mouth, intoxication (feeling lightheaded or drunk), disturbance in attention, irregular heartbeat, decrease in sleep, blurred vision, back pain, fainting, dizziness, and sleepiness.

This is not a complete list of potential adverse events associated with SUBOXONE® Film. Please see full Prescribing Information www.suboxoneREMS.com for a complete list.

*To report pregnancy or side effects associated with taking SUBOXONE® Film, please call 1-877-782-6966. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit <http://www.fda.gov/medwatch>.

For more information about SUBOXONE® Film, SUBOXONE® (buprenorphine and naloxone) Sublingual Tablets (CIII), or SUBUTEX® (buprenorphine) Sublingual Tablets (CIII), please see the respective full Prescribing Information and Medication Guide at www.suboxoneREMS.com.

SUBLOCADE™ (BUPRENORPHINE EXTENDED-RELEASE) INJECTION FOR SUBCUTANEOUS USE (CIII)

INDICATION AND HIGHLIGHTED SAFETY INFORMATION

INDICATION

SUBLOCADE is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.

SUBLOCADE should be used as part of a complete treatment plan that includes counseling and psychosocial support.

WARNING: RISK OF SERIOUS HARM OR DEATH WITH INTRAVENOUS ADMINISTRATION; SUBLOCADE RISK EVALUATION AND MITIGATION STRATEGY

- **Serious harm or death could result if administered intravenously. SUBLOCADE forms a solid mass upon contact with body fluids and may cause occlusion, local tissue damage, and thrombo-embolic events, including life threatening pulmonary emboli, if administered intravenously.**
- **Because of the risk of serious harm or death that could result from intravenous self-administration, SUBLOCADE is only available through a restricted program called the SUBLOCADE REMS Program. Healthcare settings and pharmacies that order and dispense SUBLOCADE must be certified in this program and comply with the REMS requirements.**

HIGHLIGHTED SAFETY INFORMATION

Prescription use of this product is limited under the Drug Addiction Treatment Act.

CONTRAINDICATIONS

SUBLOCADE should not be administered to patients who have been shown to be hypersensitive to buprenorphine or any component of the ATRIGEL® delivery system

WARNINGS AND PRECAUTIONS

Addiction, Abuse, and Misuse: SUBLOCADE contains buprenorphine, a Schedule III controlled substance that can be abused in a manner similar to other opioids. Monitor patients for conditions indicative of diversion or progression of opioid dependence and addictive behaviors.

Respiratory Depression: Life threatening respiratory depression and death have occurred in association with buprenorphine. Warn patients of the potential danger of self-administration of benzodiazepines or other CNS depressants while under treatment with SUBLOCADE.

Neonatal Opioid Withdrawal Syndrome: Neonatal opioid withdrawal syndrome is an expected and treatable outcome of prolonged use of opioids during pregnancy.

Adrenal Insufficiency: If diagnosed, treat with physiologic replacement of corticosteroids, and wean patient off of the opioid.

Risk of Opioid Withdrawal With Abrupt Discontinuation: If treatment with SUBLOCADE is discontinued, monitor patients for several months for withdrawal and treat appropriately.

Risk of Hepatitis, Hepatic Events: Monitor liver function tests prior to and during treatment.

Risk of Withdrawal in Patients Dependent on Full Agonist Opioids: Verify that patient is clinically stable on transmucosal buprenorphine before injecting SUBLOCADE.

Treatment of Emergent Acute Pain: Treat pain with a non-opioid analgesic whenever possible. If opioid therapy is required, monitor patients closely because higher doses may be required for analgesic effect.

ADVERSE REACTIONS

Adverse reactions commonly associated with SUBLOCADE (in ≥5% of subjects) were constipation, headache, nausea, injection site pruritus, vomiting, increased hepatic enzymes, fatigue, and injection site pain.

For more information about SUBLOCADE, the full Prescribing Information including BOXED WARNING, and Medication Guide visit www.sublocade.com.

About PERSERIS™

INDICATION

PERSERIS™ (risperidone) is indicated for the treatment of schizophrenia in adults.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
- PERSERIS is not approved for use in patients with dementia-related psychosis.

CONTRAINDICATIONS

PERSERIS should not be administered to patients with known hypersensitivity to risperidone, paliperidone, or other components of PERSERIS.

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: Increased risk of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities. PERSERIS is not approved for use in patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): Manage with immediate discontinuation and close monitoring.

Tardive Dyskinesia: Discontinue treatment if clinically appropriate.

Metabolic Changes: Monitor for hyperglycemia, dyslipidemia and weight gain.

Hyperprolactinemia: Prolactin elevations occur and persist during chronic administration. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in females and males.

Orthostatic Hypotension: Monitor heart rate and blood pressure and warn patients with known cardiovascular disease or cerebrovascular disease, and risk of dehydration or syncope.

Leukopenia, Neutropenia, and Agranulocytosis: Perform complete blood counts (CBC) in patients with a history of a clinically significant low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing PERSERIS if a clinically significant decline in WBC occurs in absence of other causative factors.

Potential for Cognitive and Motor Impairment: Use caution when operating machinery.

Seizures: Use caution in patients with a history of seizures or with conditions that lower the seizure threshold.

ADVERSE REACTIONS

The most common adverse reactions in clinical trials ($\geq 5\%$ and greater than twice placebo) were increased weight, sedation/somnolence and musculoskeletal pain. The most common injection site reactions ($\geq 5\%$) were injection site pain and erythema (reddening of the skin).

For more information about PERSERIS, the full Prescribing Information including BOXED WARNING, and Medication Guide visit www.perseris.com.

EXHIBIT 11

FILE
COPY

Supplement Review

Date of submission: March 7, 2000
Received by reviewer: March 8, 2000
Review initiated: March 8, 2000
Review completed: June 6, 2000

Designation #98-1150

Drug Name:

code name:

generic name: sustained-release Recombinant human growth hormone somatropin (rDNA origin)

trade name: ProLease rhGH

Sponsor's Name:

Genentech, Inc.

1 DNA Way

South San Francisco, CA 94080-4990

Proposed Designation:

Long term treatment of children who have growth failure due to lack of adequate endogenous growth hormone secretion.

Regulatory Status:

This product was studied under IND 47177 and approved under NDA 21-075

Background Information:

ProLease rhGH was designated in 1999 under the premise that it would be administered as one injection per month instead of one injection per day. Inherent in that designation was the assumption that not only would the drug be administered once per month, but that the adverse events profile would be similar to or better than the existing growth hormone products as would the efficacy profile. A subsequent review of ProLease rhGH by HFD-510 has shown that, at best, injection frequency is two injections per month and can be as high as four injections per month. In addition the efficacy is not comparable to daily somatropin injections and the injection site reactions with the long acting preparation are significantly increased over daily injections.

Evaluation and Recommendation:

The Orphan Drug regulations at 21 CFR 316 established that the "active moiety" or "principal molecular structural features" in an orphan drug product initially determine whether a drug is the same as a previously approved drug. This is different from the approach used for other purposes in the Federal Food, Drug, and Cosmetic Act, where a change in the formulation, the label, or the strength may make a drug a different drug. The orphan drug definition was adopted to insure that the orphan exclusivity would be meaningful, and that minor changes in a product would not permit a competitor to circumvent an innovator's exclusivity.

The regulations also recognized a need to allow for innovation and improvement in the drugs available to treat orphan diseases and conditions. This was accomplished by making it possible for a product that has the same active moiety or principal molecular structural features as a product with exclusivity to demonstrate that it is clinically superior to the approved drug, is therefore is not the "same drug" as the product with exclusivity, and can be approved despite the exclusivity. Clinical superiority can be found when the sponsor of the subsequent drug demonstrates its product has a significant therapeutic advantage in terms of safety or effectiveness when compared to the product with exclusivity.

Another way to establish clinical superiority is to demonstrate that the new product, even though it has the same active moiety or principal molecular structural features as the drug with exclusivity, makes a "major contribution to patient care." This could be the case if the newer product, for example, represents a marked improvement in how the drug is given. The example used in the preamble to the regulations is an intravenous drug that is reformulated for oral administration. 56 Fed. Reg. 3336, 3343 (January 29, 1991). Because the "major contribution to patient care" approval route could pose a significant threat to exclusivity if small changes to a drug product were allowed to circumvent an innovator's exclusivity, the Agency has maintained a very high hurdle for establishing that a product makes a major contribution to patient care. To date the only improvements which the agency has deemed "major" are a conversion from IV to oral administration, and a product which was administered once a month rather than three times a day. Changes which the agency has not deemed "major" include hospital to home administration, and premixed injectors. Each claim that a drug makes a major contribution to patient care is assessed individually, with attention given to factors such as the nature of the orphan indication, course of treatment for the indication, and benefits that could be obtained from the new product. Inherent in this analysis is the general assumption that, for example, changes in drug administration would maintain a similar or improved adverse event profile and similar efficacy.

The orphan drug regulations do not address directly the question of whether a second drug that is the same within the meaning of the Orphan Drug Act as a previously approved drug for the same indication could be eligible for orphan exclusivity. However, it has been the policy of this office to consider exclusivity for an orphan drug to have been "used up" or "spent" if the same drug already has been approved for the same orphan indication. There is no public health benefit to be garnered by granting a seven year period of exclusivity to a drug that is the same as an approved drug from another sponsor. Instead of rewarding innovation, granting exclusivity to the second product would just serve to limit the availability of competitor orphan products. It makes no difference whether the first drug to be approved for the orphan indication was also designated and received orphan exclusivity; the critical factor is that the same drug is already approved and available.

Consistent with this approach, a subsequent drug with the same active moiety or principal molecular structural features as one that is already approved would be eligible for orphan exclusivity for the same orphan indication only if the subsequent drug can demonstrate clinical superiority to the approved product. If the subsequent drug is superior, it could obtain immediate approval and orphan exclusivity. If it is not demonstrated to be superior it will not be eligible for exclusivity. Whether the subsequent drug that is not superior would be eligible for immediate

approval would depend upon whether the first product obtained orphan exclusivity, and when that exclusivity expires.

ProLease rhGH raises the issue of exclusivity for a subsequent drug that has the same active moiety or principal molecular features as a previously approved orphan product. This product is a new sustained release formulation of recombinant human growth hormone (rhGH), and contains the same principal molecular features as the other rhGH products which have expended their exclusivity. Therefore, in order for ProLease rhGH to receive orphan exclusivity, the sponsor must demonstrate that ProLease rhGH is superior to the previously approved rhGH. The sponsor made this claim based on the hypothesis that ProLease could be administered once a month instead of daily, and this represents a "major contribution to patient care".

Review of the data in NDA 21-075 has not supported the sponsor's hypothesis that one injection per month of ProLease could be substituted for daily injections of rhGH with similar efficacy and safety. At best ProLease must be administered in two (2) injections per month and the efficacy of the drug on this administration schedule is not equal to daily injections. Growth rates are significantly higher in patients receiving daily injections. In addition, the injections of ProLease are more painful and are accompanied by a higher occurrence of fat necrosis than daily injection. While ProLease does represent an alternative treatment modality, it will not replace daily injections and a number of patients which were in the clinical trial evaluating ProLease have opted to return to daily injections.

ProLease does not make a major contribution to patient care and is therefore the same drug under the orphan drug act as other approved rhGH products. If there were a rhGH with exclusivity, ProLease would not be permitted to enter the market until the exclusivity expires. However, since the exclusivity of rhGH has expired there is no barrier to the approval and sale of ProLease. Therefore, the issue is whether ProLease should receive orphan exclusivity.

Because the orphan drug regulations encourage true innovation and product improvement, the orphan designation process is very liberal about designating products if the sponsor can offer a plausible hypothesis that the proposed product is clinically superior to an existing product.¹ If at the time the application for the subsequent product is reviewed, the sponsor cannot demonstrate its product is superior to the existing drug with exclusivity, it will not be able to enter the market. In addition, when any existing orphan exclusivity expires, the subsequent product that is not clinically superior will not be eligible for exclusivity. The exclusivity for this drug has been "used up" or "spent" by the first product approved, and there is nothing to be gained in terms of providing better treatments for orphan diseases by granting a second drug that is the same a period of exclusivity.²

¹Although prior to this rhGH product, OOPD has not had occasion to deny exclusivity to an orphan drug because it is the same as a previously approved drug, the office has refused to designate a cyclosporine product for which the sponsor was unable to submit evidence that the new drug may be clinically superior to an approved cyclosporine product.

²As noted, the agency will grant designations under 21 CFR 316.20 for drugs that are otherwise the same as previously approved drugs, but for which a sponsor provides an

In this instance ProLease has not demonstrated that it makes a "major contribution to patient care." Therefore, it is the same drug as an orphan drug that has been previously approved and is not entitled to any exclusivity of its own. Although while it can enter the market, orphan exclusivity for this drug has already been spent by approved rhGH products.

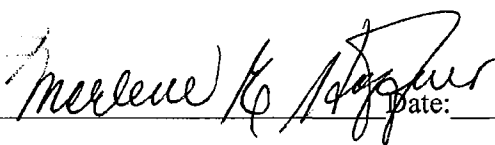
It is recommended that the sponsor be sent a letter stating the following:

After examination of your submission dated March 7, 2000 and the Medical Officer's review of NDA 21-075 the Office of Orphan Product Development has concluded that you have not demonstrated that ProLease rhGH represents a "major contribution to medical care" when compared to approved rhGH products. Therefore, ProLease is the same drug as other approved recombinant human growth hormone (rhGH) products and is not entitled to exclusivity. As you are aware, all orphan exclusivity for rhGH for the treatment of short stature due to growth hormone deficiency has expired. Although ProLease is not entitled to any exclusivity under the Orphan Drug Act, there is no current orphan drug exclusivity barring approval of ProLease.



John J. McCormick, M.D.
Medical Reviewer, Office of
Orphan Products Development
(HF-35)

Concur:



Date:

12 June '00

Marlene E. Haffner, M.D., M.P.H.
RADM USPHS
Director, Office of Orphan Products Development

cc:

HF-35/Designation File #98-1150
HF-35/Chron File

explanation of why the proposed variation may be clinically superior. If, after review of the application, the claim of clinical superiority that was the basis for the designation cannot be supported, the designation, as it applies to the drug product for which the application is submitted, is in essence prospectively withdrawn. However, the benefits (other than exclusivity) under the Orphan Drug Act the applicant received in developing the drug product will not be altered; until the agency makes its final assessment that the new product was not clinically superior, those benefits are encouraging the development of a drug that hypothetically may represent an improvement in the treatment of the orphan disease or condition.

EXHIBIT 12



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

November 13, 2012

Philip Katz, Esq.
Hogan Lovells US LLP
555 Thirteenth Street NW
Washington, DC 20004
philip.katz@hoganlovells.com

Re: Eligibility of Gralise (gabapentin) for orphan-drug exclusivity

Dear Mr. Katz:

Depomed, Inc. (Depomed) has requested that the Food and Drug Administration (FDA or Agency) reconsider its decision that Gralise (gabapentin) is not entitled to seven years of orphan-drug exclusivity for the management of postherpetic neuralgia (PHN). Depomed asserts that it was automatically entitled to such exclusivity because Gralise was the first approved drug for this indication that was also orphan designated, even though Gralise is the same drug as another gabapentin product that had already been approved for the same indication. In the alternative, Depomed asserts that Gralise is entitled to orphan-drug exclusivity because it has demonstrated clinical superiority over the previously approved drug, Neurontin (gabapentin).

We have carefully reviewed the submissions made to the Agency on these issues¹ and additional relevant materials. For the reasons set forth below, we deny Depomed's request and affirm that Gralise is not entitled to orphan-drug exclusivity.

I. Summary

Section 527(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. § 360cc)² generally grants orphan exclusivity to designated drugs upon approval,

¹ These materials include a letter from Hogan Lovells US LLP regarding orphan exclusivity for Depomed, dated September 9, 2011 ("September 2011 letter"), the arguments you advanced during our meeting with you on April 11, 2012 ("April 2012 meeting"), as well as supplemental scientific information you submitted to the Office of Orphan Products Development (OOPD) on May 10 and May 24, 2012 ("May 2012 submissions"), July 3, 2012, July 6, 2012 ("July 2012 submission"), August 6, 2012 ("August 2012 submission"), and September 25, 2012.

² In this response, references to statutory "sections" are to the FD&C Act, not the U.S. Code.

but does not address eligibility for exclusivity when the same drug has already been approved for the same orphan indication. FDA interprets this statute to confer exclusivity only to drugs that are designated and *not* the same as an already approved drug. By regulation, FDA requires sponsors of orphan-designated drugs to demonstrate the clinical superiority of their drug to the previously approved drug to show that their drug is not the same as the previously approved drug and is therefore eligible for exclusivity.^{3,4}

Gralise obtained orphan designation pursuant to section 526(a) (21 U.S.C. § 360bb) by offering a plausible hypothesis of clinical superiority over the previously approved drug, Neurontin. But, at the time of approval, Depomed was unable to demonstrate actual clinical superiority. Nor have any additional Depomed submissions demonstrated Gralise's clinical superiority over Neurontin. Gralise is therefore the "same drug" as the previously approved drug, Neurontin, and is ineligible for orphan exclusivity.

II. Factual And Procedural Background

A. Neurontin

Pfizer Inc.'s Neurontin was the first gabapentin drug approved on May 24, 2002 for management of PHN in adults.⁵ Under section 526, certain drugs for rare diseases may obtain "orphan designation," which provides valuable incentives and is a predicate for orphan-drug exclusivity. Pfizer did not seek or obtain orphan-drug designation for Neurontin, despite being eligible to do so.

There are many generic versions of Neurontin that are approved and currently marketed. Nearly 30 such A-rated generics are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book").⁶

³ In this response, references to "exclusivity" are to orphan-drug exclusivity unless otherwise noted.

⁴ The phrase "the same drug" in this response refers to the definition of sameness in the orphan drug regulations, which takes into account the chemical and clinical features of drugs and their intended use. 21 CFR 316.3(b)(13). Although this definition covers the drugs having the same intended use, we sometimes refer to "same drug for the same use" to emphasize that the intended use is the same.

⁵ Neurontin (gabapentin) was approved for other indications as early as 1993: as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients over 12 years old with epilepsy, and as adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years. Neurontin is currently approved in capsule form (100 mg, 300 mg, and 400 mg of gabapentin), in tablet form (600 mg and 800 mg of gabapentin), and as an oral solution (250 mg/5 mL gabapentin). The FDA-approved Neurontin labeling is available at

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_Approval_History. Because Gralise is approved for its orphan indication, it may be prescribed by physicians (but not promoted by Depomed) for off label uses, including other uses for which only Neurontin is approved even though the two products are not therapeutically equivalent. It is also well known that part of the market for gabapentin drugs represents uses for which no gabapentin product is approved by FDA.

⁶ "A" rated generics have been determined to be therapeutically equivalent to the innovator or reference listed drug, and may be fully substituted for that product. See generally Orange Book Preface, available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm>. At least 20 such generics were approved before the date that Gralise was approved (January 28, 2011); at least nine gabapentin generics have been approved after the date of Gralise's approval.

B. Gralise

Gralise contains the same active moiety as Neurontin but is a slightly different formulation that incorporates different inactive ingredients and gastric-retentive technology, which you describe as a “polymer technology that enables the tablet to expand in the stomach when taken with the evening meal.” September letter, p. 18. By virtue of this new formulation, FDA views Gralise as a *different drug product* from Neurontin despite being *chemically the same drug* within the meaning of the orphan drug regulations.⁷ This new formulation allows Gralise to be taken once-daily instead of Neurontin’s three daily doses. Whereas Neurontin is to be titrated up to a dosage of 1800 mg divided into three daily doses (TID) taken with or without food,⁸ Gralise is to be titrated to an 1800 mg dose taken orally, once-daily.⁹

Gralise’s former sponsor¹⁰ requested orphan designation to manage PHN on December 21, 2006.¹¹ FDA ultimately granted designation on November 8, 2010, after several rounds of deficiency letters that are detailed in your September 2011 letter (pp. 3-6). Many of these deficiency letters, and the sponsor’s responses, reflected a disagreement as to the regulatory requirements for designation. The crux of this disagreement was whether the designation request for Gralise needed to contain a plausible hypothesis of clinical superiority over Neurontin, the same drug already approved for the same orphan use. Consistent with its long-standing interpretation of the orphan drug regulations, the Office of Orphan Products Development (OOPD) maintained that designation for Gralise could not be obtained absent such a plausible hypothesis of clinical superiority, per 21 CFR 316.20(a) and (b)(5). The sponsor countered that, under 21 CFR 316.24, FDA must grant designation unless any of the reasons specified at 21 CFR 316.25 applies – and the latter regulation does not list “failure to include a plausible hypothesis of clinical superiority where the same drug is already approved for the same use” as a reason for refusing designation. FDA disagreed with this interpretation of its regulations, as described further below in Section IV.B.

The sponsor ultimately provided a hypothesis of greater safety for Gralise over Neurontin, which FDA deemed plausible. “The comparison of the incidence of adverse

⁷ Different drug products (*i.e.*, with different dosage forms or different inactive ingredients) may incorporate the same drug (*i.e.*, have the same active moiety or principal molecular structural features). Compare 21 CFR 314.3(b) (defining “drug product”) with 21 CFR 316.3(b)(13) (defining “same drug”).

⁸ Neurontin PI, Dosage and Administration, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020235s050,020882s035,021129s033lbl.pdf (label approved by FDA on 8/10/2011).

⁹ Gralise PI, Dosage and Administration, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022544s006lbl.pdf (label approved by FDA on 1/31/2012).

¹⁰ As detailed in the September 2011 letter, ownership of Gralise changed in these intervening years, from Depomed to Solvay Pharmaceuticals (later acquired by Abbott Products, Inc. (Abbott)), and again back to Depomed. September 2011 letter, at pp. 3-6. For ease of reference, we refer to the “sponsor” throughout this response to refer to the entity that owned Gralise at the relevant time, whether Depomed, Abbott, or Solvay.

¹¹ There is no dispute in this matter that PHN qualifies as a rare disease or condition under section 526.

events of [Gralise] to the reported incidence of adverse events of Neurontin, found in the Neurontin package insert, is adequate for supporting a *plausible hypothesis* that [Gralise] is clinically superior to the currently marketed form of gabapentin, based on better safety[,] for the purpose of orphan[-]drug designation.” OOPD designation letter, November 8, 2010 (emphasis added). The designation letter advised, however, that clinical superiority over Neurontin would have to be *demonstrated* in order for Gralise to obtain orphan exclusivity upon approval.

FDA approved Gralise 300 mg and 600 mg tablets for the management of PHN on January 28, 2011 (NDA 22-544). The Gralise NDA relied on the Agency’s previous finding of safety and efficacy for Neurontin; Neurontin was the reference listed drug for the Gralise application.¹² As FDA’s summary review explained, “[Because] this [Gralise] application is relying on the Agency’s previous finding of safety and efficacy for Neurontin, which carries an indication for PHN, during development the division agreed that only a single adequate and well-controlled study would be required to establish the efficacy of the new formulation.”¹³ To meet this requirement, the Gralise sponsor submitted efficacy data from a randomized, double-blind, placebo-controlled study in 452 PHN patients treated with either Gralise 1800 mg once daily or placebo in an approximately 1:1 ratio for a total of 11 weeks.¹⁴ This efficacy study was considered essential to and supported approval of the new formulation. Accordingly, Gralise received three years of market exclusivity following the date of NDA approval. This three-year exclusivity bars FDA from approving any ANDA or 505(b)(2) application by another party that relies on the information supporting the conditions of approval of Gralise until January 28, 2014. Sections 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act; 21 CFR 314.108(b)(4).¹⁵

FDA did not grant orphan exclusivity to Gralise upon approval because Gralise was not demonstrated to be clinically superior to Neurontin and, therefore, under FDA’s interpretation of the statute, was the “same drug” as Neurontin and not eligible for exclusivity.¹⁶

¹² This application was submitted in accordance with section 505(b)(2) (21 U.S.C. § 355(b)(2)) (“505(b)(2) application”).

¹³ NDA 22-544 Summary Review, p. 3, *available at*

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022544Orig1s000SumR.pdf. The applicant submitted the results of three efficacy trials, one Phase 2 and two Phase 3 studies. The Phase 2 study and one of the Phase 3 studies failed to demonstrate a statistically significant treatment effect. *Id.*, p. 11.

¹⁴ *See id.* For the successful Phase 3 study, the primary efficacy endpoint was the mean change in average daily pain scores from the baseline week to the final week of the efficacy treatment period for patients treated with Gralise compared to placebo. The analysis of efficacy demonstrated a statistically significant superiority for Gralise compared to placebo.

¹⁵ A three-year exclusivity is granted for a drug product that contains an active moiety that has been previously approved if the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the sponsor that were essential to and supported approval of the application. Changes in an approved drug product that affect its active ingredient(s), strength, dosage form, route of administration, or conditions of use, for example, may be granted exclusivity if clinical investigations are essential to and support approval of the application containing those changes.

¹⁶ We note that FDA approved a prodrug of gabapentin for management of PHN on June 6, 2012. This prodrug, Horizant, is an extended-release formulation of gabapentin enacarbil. It received orphan

C. Challenges To FDA's Exclusivity Decision

Following approval, Depomed challenged FDA's decision that Gralise was not entitled to orphan exclusivity on two separate bases. First, by letter dated September 9, 2011, Depomed asserted that the plain language of the statutory provision in section 527 compelled exclusivity because Gralise was designated and approved, even though Gralise was not demonstrated to be clinically superior to Neurontin. *See* September 2011 letter, pp. 7-15.

Second, Depomed provided additional evidence to support its claim that Gralise was clinically superior to Neurontin. In these submissions, Depomed alleged that Gralise was clinically superior to Neurontin either by providing greater safety or by making a major contribution to patient care.¹⁷

On September 25, 2012, while FDA and Depomed were still discussing the possibility that Gralise might receive orphan exclusivity predicated on a clinical superiority showing,¹⁸ Depomed sued FDA in the United States District Court for the District of Columbia seeking declaratory, injunctive, and other relief, for FDA's failure to recognize orphan exclusivity for Gralise.¹⁹ This complaint reiterated many of the legal arguments in the September 2011 letter and also included allegations not previously raised before the Agency. *See* Complaint ¶¶ 51-58. FDA has reviewed these new allegations and describes its findings and analysis below, in Section IV.C.

exclusivity without having to demonstrate clinical superiority over the previously approved versions of gabapentin because it was not considered to be the "same drug" under 21 CFR 316.3(b)(3). It was considered to have a different active moiety owing to the chemical structure of its active ingredient. For a description of Horizant's chemical properties, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022399s003lbl.pdf (Section 11, Description).

¹⁷ For a list of these submissions, see *supra* note 1.

¹⁸ OOPD was in e-mail and phone communication with Depomed on the morning of September 25, 2012, concerning the design of the physician survey that Depomed had submitted in support of its contention that Gralise is clinically superior to Neurontin by providing a major contribution to patient care. For further discussion of this physician survey, see Section V.B of this response.

¹⁹ This lawsuit was filed even though existing three-year exclusivity, to which Depomed is entitled as described on page 4 of this response, would bar approval of any generic copy of its product until early 2014 and even though ongoing patent litigation appears likely to delay such approval even longer. *See* Depomed, Inc. Form 10-Q, 8/3/2012, p. 32, *available at* <http://investor.depomedinc.com/phoenix.zhtml?c=97276&p=irol-SECText&TEXT=aHR0cDovL2lyLmludC53ZXN0bGF3YnVzaW5lc3MuY29tL2RvY3VtZW50L3YxLzAwmDExMDQ2NTktMTItMDU0MTU0L3htbA%3d%3d>. This document describes patent suits involving seven generic applications for copies of Gralise and states that, with respect to the first three such applications, "We commenced the lawsuit within the 45 days required to automatically stay, or bar, the FDA from approving the ANDAs for 30 months or until a district court decision that is adverse to the asserted patents, whichever may occur earlier. Absent a court order, the 30-month stays are expected to expire in July 2014 and August 2014." For the additional suits the same statement is made with the exception that the expected expiration is stated to occur, respectively, in September, October, and November 2014.

III. Statutory And Regulatory Authorities

In 1983, Congress enacted the Orphan Drug Act (Public Law 97-414) to provide incentives to develop drugs to treat rare diseases and conditions. The Orphan Drug Act included amendments to the FD&C Act (sections 526-528). As defined in section 526(a) (as amended by a 1984 amendment to the statute), a rare disease or condition includes any disease or condition that affects fewer than 200,000 persons in the United States. Drugs for rare diseases or conditions are “commonly referred to as ‘orphan drugs,’” Congress explained, because “[t]hey generally lack a sponsor to undertake the necessary research and development activities to attain their approval by the [FDA].” H.R. Rep. 97-840, Pt. 1, at 6 (1982). Rare diseases and conditions “affect such a small number of persons that there is virtually no commercial value to any drug which is useful against them. . . .” *Id.* To mitigate these commercial disincentives and foster the development of drugs that would not otherwise be developed and approved, Congress created a system to reduce the cost and increase the potential reward for developing orphan drugs. “The legislative history is replete with references to the fundamental need to provide treatment for *presently untreated patients*.” *Genentech v. Bowen*, 676 F. Supp. 301, 312 (D.D.C. 1987) (emphasis added).

Among the incentives provided by the Orphan Drug Act are tax credits for clinical testing, research grants, and the possibility of seven years of market exclusivity. Orphan-designated drugs are also exempt from application user fees.²⁰ Following enactment of the Orphan Drug Act in 1983, FDA’s program has successfully enabled the development and marketing of more than 400 drugs for rare diseases and conditions.²¹ By contrast, fewer than ten such products supported by industry came to market between 1973 and 1983.²²

A drug must first be designated as an orphan drug to be potentially eligible for orphan exclusivity upon approval. *See* sections 526(a) & 527(a); 21 CFR 316.31 and 316.34. In order to obtain designation, the drug’s sponsor must submit to FDA a request for designation that includes, among other things, a description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed. 21 CFR 316.20(b)(3); *see generally* 21 CFR 316.20 and 316.21. When a drug is otherwise the same (*i.e.*, contains the same active moiety or principal molecular structural features²³) as an already approved orphan drug for the same use, the request for designation must contain “a plausible hypothesis of clinical superiority” over the previously approved drug. 21 CFR 316.20(a) and (b)(5).

Section 527 instructs FDA not to approve “another application . . . for *such drug* for such disease or condition” (emphasis added) for seven years from the date that a

²⁰ This application user fee exemption was enacted as part of the Prescription Drug User Fee Act of 1992 (PDUFA), since reauthorized.

²¹ *See* Developing Products for Rare Diseases & Conditions, *available at* <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>.

²² *See id.*

²³ *See* 21 CFR 316.3(b)(13).

particular designated drug is approved, with certain exceptions not relevant here.²⁴ Congress provided no guidance on what “such drug” means in this context. *See* 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992); *Baker Norton Pharms. v. FDA*, 132 F. Supp. 2d 30, 36 (D.D.C. 2001) (“Given the multiple definitions of the term ‘drug,’ and the different purposes that various statutory provisions can serve, the Court cannot find that the definition of ‘drug’ in § 360cc(a) is clear and unambiguous.”). After extensive consideration of the Orphan Drug Act’s text and purpose, FDA defined “such drug” through implementing regulations defining sameness. *See* 56 Fed. Reg. 3341 (Jan. 29, 1991); 57 Fed. Reg. 62076.

Under these regulations, FDA will not approve the “same drug,” as defined in 21 CFR 316.3(b)(13), for a period of seven years. Two drugs that are chemically the same and indicated for the same use may nevertheless not be the “same drug” if the second drug is “clinically superior” to the previously approved drug, as defined in 21 CFR 316.3(b)(3). A sponsor may demonstrate clinical superiority by showing that its drug provides a “significant therapeutic advantage” by providing greater effectiveness or safety or by making a “major contribution to patient care” as compared to the previously approved drug that is chemically the same. 21 CFR 316.3(b)(3). A clinically superior drug may be approved with its own term of orphan exclusivity – and notwithstanding any existing exclusivity for the previously approved drug that is chemically the same – because FDA interprets a clinically superior drug as not being within the meaning of the term “such drug” in section 527. *See* 56 Fed. Reg. 3338 (describing these implementing regulations as fulfilling a main purpose of the Orphan Drug Act, “to stimulate innovation in developing treatments for patients with rare diseases and conditions”). These implementing regulations have been upheld upon judicial review as a reasonable construction of the statute. *Baker*, 132 F. Supp. 2d at 36.

If a sponsor fails to demonstrate clinical superiority of a drug that is chemically the same as a previously approved drug and for the same use, the subsequent drug would be considered the “same drug” and so fall within the meaning of “such drug” in section 527. It could not be approved during the pendency of the first-in-time drug’s exclusivity, if any, and when approved would not receive a separate, additional term of orphan exclusivity. This is because FDA interprets section 527 as according orphan exclusivity to a designated drug only the first time that drug is approved for the orphan use. *See* 56 Fed. Reg. 3341 (“FDA interprets the act to accord [orphan] exclusive approval only to the first drug approved.”).

We note that the clinical superiority requirements are different at the designation and approval stages, respectively. At the designation stage, the sponsor needs to provide a *plausible hypothesis* of clinical superiority, as described above. At the approval stage,²⁵ however, the sponsor must *demonstrate* clinical superiority over the previously approved

²⁴ These exceptions involve the sponsor’s inability to assure availability of sufficient quantities of the approved drug and the sponsor’s written consent for other applications to be approved during the exclusivity period. Section 527(b).

²⁵ In this context, the terms “at the approval stage” or “upon approval” do not preclude the possibility of demonstrating clinical superiority in a supplemental submission for the drug, after approval.

drug in order to obtain orphan exclusivity and to be approved despite any existing orphan exclusivity for the previously approved drug. *See* 21 CFR 316.3(b)(3) (“Clinically superior means that a drug *is shown to provide* a significant therapeutic advantage”) (emphasis added); 56 Fed. Reg. 3343 (“the burden of proof (including the burden of production of evidence and the burden of persuasion of FDA) [is] on the sponsor of the subsequent drug who is contending that its drug is different”). This difference in clinical superiority requirements is intended to encourage the development of improved versions of existing drugs while still protecting the value of any orphan exclusivity. The former is achieved through liberally granting designation based on a plausible hypothesis of clinical superiority, allowing drugs to benefit from development incentives that flow from designation, including tax credits and exemption from application user fees. The latter is achieved through reserving exclusivity for a subsequent drug only if the subsequent drug is shown to provide a significant therapeutic advantage compared to the existing product. *See* 56 Fed. Reg. 3338, 3340.

Under this clinical superiority framework, FDA applies the same standard for granting orphan exclusivity whenever the same drug is already approved, whether or not the previously approved drug has orphan exclusivity. In this way, the framework furthers the aim of the Orphan Drug Act, to promote development and innovation of orphan drugs that have not already been developed and approved. *See* H.R. Rep. 97-840, Pt. 1, at 6 (1982); 56 Fed. Reg. 3338; *Genentech*, 676 F. Supp. at 305-06, 312. If a sponsor is able to demonstrate clinical superiority over a drug that is previously approved with or without exclusivity, that sponsor would receive its own orphan exclusivity and would not be blocked by any orphan exclusivity attaching to the previously approved drug. Conversely, even if the previously approved drug does not have exclusivity, the sponsor of the drug seeking exclusivity will not obtain exclusivity if it cannot demonstrate clinical superiority over the previously approved drug. Thus, the exclusivity status of the previously approved drug – whether it has, had, or never had exclusivity – does not affect the clinical superiority requirements. *See* 76 Fed. Reg. 64868, 64870 (Oct. 19, 2011) (“If the same drug has already been approved for the orphan disease or condition, *with or without orphan exclusivity*, designation [absent a plausible hypothesis of clinical superiority] would be inappropriate because it would be inconsistent with the primary purpose of the Orphan Drug Act, which is to provide incentives to develop promising drugs for rare diseases or conditions that would not otherwise be developed and approved.”) (emphasis added).²⁶

²⁶ This preamble explains, “In the absence of a clinical superiority hypothesis, the Agency does not interpret the orphan-drug regulations to permit orphan designation of a drug that is otherwise the same as a drug that is already approved for the orphan use, either where the approved drug received orphan-drug exclusive approval (even after such drug’s exclusivity period has run out) *or where the approved drug was not previously designated as an orphan drug and thus did not receive orphan exclusive approval.*”) 76 Fed. Reg. 64870 (emphasis added).

IV. Exclusivity Is Available Only If The Same Drug Has Not Been Previously Approved For The Orphan Indication

A. The Statute Does Not Automatically Accord Orphan Exclusivity To All Designated Drugs Upon Approval

You contend that Gralise is “automatically” entitled to orphan exclusivity under section 527 because it is a drug that received designation and was then approved for marketing, even though Neurontin was the same drug as Gralise and had already been approved for the same orphan indication. *See* September 2011 letter, pp. 13-15. But the statute cannot be logically read to confer exclusivity to every designated drug that gets approved, as your argument would require.

The statute generally confers exclusivity by prohibiting FDA from approving later drugs after a previous drug has been designated and approved. “[I]f the Secretary [] approves an application . . . for a drug designated under section 526 . . . the Secretary may not approve another application . . . for *such drug* . . . until the expiration of seven years from the date of the approval of the approved application.” Section 527(a) (emphasis added). Courts construing this statute have held “such drug” to be ambiguous, and have upheld FDA’s regulatory scheme to require a showing of clinical superiority over a previously approved drug in order for the clinically superior drug to not be blocked by another sponsor’s exclusivity and to obtain its own period of exclusivity. *See Baker*, 132 F. Supp. at 37.

Section 527(a) is also ambiguous on the question whether a drug may be eligible for exclusivity when *another* drug that is the same has already been approved. *See* section 527(a) (referring to an approved drug and unapproved applications for such drug, but not to any drugs approved previously to the approved drug). Under FDA’s interpretation, any such previously approved drug matters and precludes exclusivity absent a showing of clinical superiority because sponsors could otherwise (1) obtain infinite, successive seven-year periods of exclusivity for the same drug for the same use (when the previously approved drug had exclusivity), or (2) obtain an exclusivity period for a drug without providing any benefit to patients over previously approved therapies (when the previously approved drug did not have exclusivity).

You raise the precise issue of whether a drug may be eligible for exclusivity when another same drug has already been approved and did not have exclusivity. Because the statute does not address that issue, FDA may interpret it, and FDA concludes that a designated drug will receive orphan exclusivity upon approval *only if the same drug has not been previously approved for the same orphan use*. *See* 56 Fed. Reg. 3338, 3341 (Jan. 29, 1991) (“FDA interprets the act to accord [orphan] exclusive approval only to the first drug approved.”). This construction implements the exclusivity period as written, is consistent with FDA’s regulatory framework, and best effectuates Congress’ aim in enacting the Orphan Drug Act, to encourage the development and innovation of

drugs that would not otherwise be developed and approved – not to encourage minor modifications to already approved drugs that confer no meaningful benefit to patients.

You concede that if an orphan-designated drug is the same drug, for the same use, as a drug that is already approved and currently enjoying orphan exclusivity, FDA cannot approve the subsequent drug for the remainder of the exclusivity period (except in limited circumstances).²⁷ See September 2011 letter, pp. 8-10. But, you argue, the statute requires that in all circumstances where FDA is in a position to approve an orphan-designated drug, it must simultaneously grant orphan exclusivity. See *id.*

FDA recognizes that the statute could be read to require a grant of exclusivity to *every drug* that is both designated and approved. But ignoring the significance of any same previously approved drug would turn the statute on its head by allowing a windfall of exclusivity to sponsors whose drugs are the same as previously approved drugs and provide no meaningful benefit to patients.²⁸ Under your argument, the second drug would be entitled to exclusivity even when the previously approved drug had orphan exclusivity and this exclusivity has run, and the second drug was not clinically superior to the previously approved drug. The same drug would thus receive serial awards of orphan exclusivity for the same use (“evergreening”): a second-in-time drug would be approved with its own orphan exclusivity upon expiration of the first-in-time drug’s orphan exclusivity, even when it is the same drug as this first-in-time drug and has been approved for the same use. Under this construction, there could be a situation in which there would be only one drug on the market for seven years, only two drugs on the market for 14 years, only three drugs on the market for 21 years, etc.²⁹

Such “evergreening” would allow orphan exclusivity to be extended indefinitely for the same drug without any meaningful benefit to patients, a result at odds with the seven-year period provided by the statute. See *Baker*, 132 F. Supp. at 37 (noting with approval that, under FDA’s interpretation, “market exclusivity rights are limited in time to seven years, and granted only for a particular drug for a particular use”). Congress would not have prescribed a definite period of exclusivity and at the same time provided for means to indefinitely extend that period, delaying generic competition in perpetuity. Indeed, the legislative history reflects this by stating that even if multiple sponsors get designation for the same drug, “only the first sponsor to be approved is awarded the seven year market exclusivity for that drug for the approved use.” H.R. Rep. 100-473, at 6 (1987).

²⁷ See *supra* note 24.

²⁸ A third possible interpretation of section 527 would grant exclusivity to a designated drug upon approval only if it is *the first designated drug* to be approved for that use (*i.e.*, either the first time such a drug is approved or, if not the first time, if the sponsor(s) of the previously approved drug(s) chose not to seek orphan designation or exclusivity). This interpretation would similarly be at odds with the purpose of the statute by granting the benefit of exclusivity to companies like Depomed that do not develop drugs for new orphan indications but simply wait until someone else does and then develop commercially viable but not clinically superior alternative formulations of those same drugs.

²⁹ It is uncertain how FDA would implement Depomed’s interpretation of the statute if multiple designated drugs were potentially eligible for approval upon expiration of the first-in-time drug’s exclusivity.

Even when, as here, the first approved drug did not have orphan designation or exclusivity, awarding orphan exclusivity to a second-in-time drug that has not been shown to be clinically superior to the first approved drug would be incompatible with the core objective of the Orphan Drug Act, to encourage development of drugs that would not otherwise be developed and approved. *See* Section III, *supra*. To award Gralise orphan exclusivity in this instance, despite there being at least 20 versions of the same drug approved at the time of Gralise's approval, would not serve this statutory purpose.

Your interpretation of the statute is also inconsistent with the decisions of courts that have had occasion to address orphan exclusivity. Courts have interpreted section 527 as awarding exclusivity to only the first orphan drug approved for the orphan use. *See Genentech*, 676 F. Supp. at 304 (orphan exclusivity "is reserved for the first manufacturer to receive full FDA approval of its drug as safe and effective for commercial sale," even if multiple drugs have orphan designation); *cf. Baker*, 132 F. Supp. 2d at 31 (if two drugs are the same under FDA regulations, "the second drug may not be approved for market exclusivity"). Although courts have not addressed this precise issue at hand – where the sponsor of the first-in-time drug chose not to pursue orphan designation and orphan exclusivity despite being eligible – the statutory interpretation upon which you rely is inconsistent with the understanding of Congress, the courts, and FDA: namely, that orphan exclusivity is not awarded to all designated drugs upon approval, but is reserved for only those drugs that are not the same as previously approved drugs.

Under your theory of exclusivity, Depomed would obtain a seven-year exclusivity period vis-à-vis all drugs that are the "same" as Gralise, including all generic Gralise and generic Neurontin products. *See* 21 CFR 316.3(b)(12),(13). Gralise would obtain such broad exclusivity even though it has not demonstrated that that it provides any clinical benefit over Neurontin.³⁰ This result could lead to withdrawal of approval of at least nine generic versions of Neurontin that have been approved since Gralise was approved (January 28, 2011).³¹ It would also prevent any additional approvals of generic versions of Neurontin until January 28, 2018 (*i.e.*, because Neurontin would be considered the same drug as Gralise), even though there were over 20 generic versions of Neurontin already approved by the time that Gralise was approved.

Your argument that FDA regulations at 21 CFR 316.3(b)(12), 316.31(a), and 316.34(a) apparently mirror the statute in recognizing automatic orphan exclusivity upon

³⁰ We note that, in order to obtain approval, the Gralise sponsor (Depomed's predecessor) relied on the Agency's previous finding of safety and efficacy for Neurontin and, because of that reliance, was required to produce only one clinical study showing the effectiveness of its product. Ultimately Depomed submitted the results of three studies, but only one (a randomized, double-blind, placebo-controlled study in 452 PHN patients treated with either Gralise or placebo) was found to show effectiveness. This study showed that Gralise is more effective than placebo; it did not compare Gralise to any already approved versions of gabapentin, including Neurontin.

³¹ Depomed does not appear to be seeking the benefit of this breadth of exclusivity (*see* Complaint ¶ 11, referring only to pending ANDAs that "would compete directly with Gralise") and could selectively waive any such exclusivity if it were to prevail on this theory.

approval of any designated drug is equally misplaced.³² See Complaint ¶¶ 28-31. You are interpreting these regulatory provisions in isolation from the remainder of the orphan drug regulations, and your interpretation could dismantle the clinical superiority framework. The provisions you cite, when read in context, provide that if designation is predicated on a clinical superiority hypothesis, clinical superiority would need to be demonstrated upon approval for the drug to receive exclusivity. See also 21 CFR 316.3(b)(3) & (13); 316.20. Under your proposed interpretation, the requirement for a plausible hypothesis of clinical superiority in 21 CFR 316.20 would make no sense – if clinical superiority must be hypothesized, then by definition it must be proven. Recognizing exclusivity on the basis of clinical superiority that is not proven, or even proven wrong, would be illogical. Moreover, to read the regulations as automatically awarding such exclusivity would lead to results counter to the Orphan Drug Act, described above, including “evergreening” of exclusivity and allowing a windfall of exclusivity to sponsors whose drugs are the same as previously approved drugs and provide no meaningful benefit to patients.

For all of the foregoing reasons, Gralise is not automatically entitled to exclusivity simply because it is a designated drug that is approved for marketing.

B. Under FDA Regulations, The Gralise Designation Request Required A Plausible Hypothesis Of Clinical Superiority Over Neurontin³³

You argue that section 526(a) requires FDA to designate a product as an orphan drug if the sponsor timely submits a request for designation and demonstrates that the drug (1) “is being or will be investigated for a rare disease or condition” and (2) if approved, would be approved for that disease or condition. If your argument were adopted, any drug that met these statutory criteria would automatically receive orphan designation, regardless of whether the regulatory requirements for designation are met (e.g., regardless of whether the request includes a plausible hypothesis of clinical superiority where the drug is otherwise the same as an already approved drug). Your argument thus disregards the regulatory requirements for designation.

The FD&C Act expressly provides FDA with the authority to promulgate regulations in this very context. Section 526(d) provides that FDA “shall by regulation promulgate procedures for the implementation of subsection (a).”³⁴ Relying on this expressly delegated rulemaking authority, FDA issued regulations in 1992. 57 Fed. Reg. 62076 (codified at 21 CFR part 316). These regulations define “same drug” and require

³² It is true that, when a drug is eligible for orphan exclusivity pursuant to FDA’s regulatory scheme, it automatically receives such exclusivity upon approval with or without written notice from FDA. 21 CFR 316.31(a), 316.34(a). Here, the issue is whether Gralise is even eligible for exclusivity in the first place.

³³ We note that the Gralise sponsor already received designation and FDA is not proposing to revoke designation, whether or not Gralise receives orphan exclusivity. The question whether the Gralise designation request required a plausible hypothesis of clinical superiority is therefore moot. It has no bearing on whether Gralise is automatically entitled to orphan exclusivity upon approval. We are nonetheless including this discussion for the sake of completeness, to respond to your arguments in the September 2011 letter and related submissions.

that designation requests for drugs that are otherwise the same as already approved drugs include a plausible hypothesis of clinical superiority, as described above. These regulations defining “same drug” have been upheld as a permissible construction of the statute. *Baker*, 132 F. Supp. 2d at 36. Because FDA acted within its expressly delegated authority in issuing these regulations, the regulations are entitled to deference. *See Arent v. Shalala*, 70 F. 3d 610, 615 (D.C. Cir. 1995). We thus find unpersuasive your argument that Gralise was by statute entitled to designation regardless of whether the regulatory requirements for designation were met.

You further maintain that FDA did not have authority under its orphan drug regulations to require that the Gralise designation request include a plausible hypothesis of clinical superiority over Neurontin. September 2011 letter, p. 11. By your reasoning, FDA could not deny Gralise’s designation based solely on a failure to include such a hypothesis, because that failure – when the previously approved drug did not have orphan-exclusive approval, as is the case here – is not expressly listed at 21 CFR 316.25 (“Refusal to grant orphan-drug designation”). You maintain that section 316.25 circumscribes FDA’s ability not to grant designation to the reasons expressly listed.

FDA disagrees. Nothing in section 316.25 supports the conclusion that the list of reasons for refusing to grant an orphan designation request contained in this section is exclusive. Instead, that regulation states that FDA will refuse to grant a designation request if certain stated reasons apply; it does not state all potential reasons for declining designation. In particular, 21 CFR 316.25 does not reiterate all of the eligibility criteria for designation that are listed elsewhere in the statute and in part 316. These eligibility criteria include that the designation request be submitted before submission of the marketing application, as is required by section 526(a) and 21 CFR 316.23(a), and that the product be a drug, as is required by section 526(a) and 21 CFR 316.20. The statute and regulations thus identify eligibility criteria for designation that are not explicitly reiterated as grounds for refusing designation at section 316.25. Under FDA’s long-standing interpretation, a designation request that failed to meet any of these eligibility requirements would be denied on this ground alone without resort to section 316.25. This interpretation is bolstered by section 316.29(a)(3), which allows for revocation of designation if the drug was not in fact eligible for designation at the time of the submission of the request. Thus, particularly when read in context, section 316.25 does not purport to contain an exhaustive list of deficiencies that would require FDA to deny an orphan-drug designation request.

FDA has consistently interpreted 21 CFR 316.20(a) and (b)(5), in particular, as requiring that a designation request include a plausible hypothesis of clinical superiority whenever the same drug is already approved for the same use, regardless of whether this same drug has, had, or never had orphan exclusivity: *i.e.*, where the drug is “otherwise the same drug as an already approved orphan drug.” “Orphan drug” is defined at section 316.3(b)(10) as a drug for a rare disease or condition; *it does not include any requirement*

³⁴ Courts have assumed that the authority to promulgate “procedures” includes the authority to substantively define terms such as “drug.” *See Genentech*, 676 F. Supp. at 312.

that the drug receive orphan designation or orphan exclusivity.³⁵ The text of section 316.20(a) specifies that “a sponsor of a drug that is otherwise the same drug as an already approved orphan drug may *seek and obtain* orphan-drug designation for the subsequent drug for the same rare disease or condition *if it can present a plausible hypothesis* that its drug may be clinically superior to the first drug” (emphasis added). It follows from this “seek and obtain” language that, absent such a hypothesis, designation can be neither sought nor obtained. Indeed, the Common EMEA/FDA Application Form for Orphan Medicinal Product Designation (Form FDA 3671) states as much. It provides that sponsors may request designation from FDA for “a *potentially clinically superior* medicinal product containing the same active substance as one in an *already authori[s]ed medicinal product* for the same orphan use” (emphasis added), indicating that clinical superiority must be hypothesized whenever the same drug is approved with or without exclusivity.³⁶ It is FDA’s long-held position that a request that fails to meet this threshold eligibility requirement will be denied on this ground alone and will not fall within the ambit of sections 316.24 (“Granting orphan-drug designation”) and 316.25 (“Refusal to grant orphan-drug designation”). This has been FDA’s consistent position since the regulations took effect on January 28, 1993.³⁷ FDA’s interpretation of its own regulations in this manner is entitled to great deference. *Sigma-Tau Pharms. v. Schwetz*, 288 F. 3d 141, 146 (4th Cir. 2002); see *Thomas Jefferson Univ. v. Shalala*, 512 U.S. 504, 512 (1994); *Udall v. Tallman*, 380 U.S. 1, 16 (1965); *Bowles v. Seminole Rock & Sand Co.*, 325 U.S. 410, 413-414 (1945).

In your contrary interpretation of the regulations, Depomed points to section 316.25(a)(3), which addresses a situation in which the sponsor of a previously approved drug sought and obtained orphan-drug designation and exclusivity. The Agency did not, in drafting that provision, focus on the rare instances where the sponsor of the previously approved orphan drug did not seek orphan-drug designation or exclusivity. This situation has presented itself on only a few occasions, though FDA has reviewed thousands of requests for designation under the statute. There is nothing to suggest that FDA, in drafting the regulations, intended the requirement for a plausible hypothesis of clinical superiority not to apply in the latter circumstance – especially in light of the threshold eligibility requirements in section 316.20. (As noted and described further below, when this situation has presented itself in designation requests, FDA has acted consistently with the position it is taking here.)

³⁵ It is worth noting that this definition of “orphan drug” is consistent with how Congress used the term “orphan drug” in enacting the Orphan Drug Act, to refer to drugs intended for use by such a small population that they have little to no commercial value and hence generally lack sponsors (*i.e.*, are “orphans”). H.R. Rep. 97-840, Pt. 1, at 6 (1982).

³⁶ The version of this form approved in 2011 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048361.pdf>. The earlier version of this form, approved in 2008 (see 73 Fed. Reg. 2504), contained the same cited excerpt.

³⁷ To FDA’s knowledge, this interpretation of the regulations has been consistent since at least the effective date of the final rule, January 28, 1993. See Section IV.C, *infra*. The Kogenate example cited by Depomed in its complaint (see Section IV.C of this response) is not relevant to this point because, at the time that the Kogenate sponsor submitted a request for designation, the same drug had not yet been approved for marketing for the orphan indication in question. The designation request for Kogenate thus did not require a plausible hypothesis of clinical superiority. Note also that this designation request was submitted in 1989, several years before the final rule issued.

Finally, we note that your arguments, by their own terms, fail to advance your claim. If we were to adopt your proposed interpretation of the regulations – in particular, your interpretation of the term “orphan drug” as meaning only drugs with orphan exclusivity (September 2011 letter, p. 12) – then the sponsor of Gralise would not have been eligible even to *request* orphan designation under section 316.20(a), with or without a clinical superiority hypothesis. The text of section 316.20(a) reads:

A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same as an already approved orphan drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug.

Were we to interpret “orphan drug” as narrowly as you urge, then the sponsor for Gralise would not have fit into any of the above-specified categories: (1) Gralise was not a “previously unapproved drug” because the same drug has already been approved numerous times; (2) management of PHN was not a “new orphan indication for an already marketed drug,” as the already-marketed drugs were approved for management of PHN; and (3) if we were to accept your interpretation that the term “approved orphan drug” means only “approved orphan drug with orphan-drug exclusivity,” Gralise was not otherwise the same as an already approved orphan drug, because the already approved drug never had orphan exclusivity. Your proposed interpretation thus excludes Gralise from the categories of drugs that are eligible to *submit* a designation request, let alone obtain designation. It is only by virtue of the broad definition of “orphan drug” under section 316.3(b)(10) that the Gralise sponsor was even eligible to seek designation under section 316.20(a). You are thus in the untenable position of arguing that “orphan drug” is both broad and narrow in section 316.20: broad for the purpose of determining which sponsors can submit designation requests, but narrow for the purpose of determining which designation requests require a plausible hypothesis of clinical superiority.

FDA acknowledges that the situation presented here, in which a company does not develop a new drug for a new orphan indication but nevertheless seeks to obtain orphan-drug exclusivity for its version of the already approved drug because the original developer of the drug had not done so, does not arise often. These circumstances have arisen on only a handful of occasions in nearly 30 years and were not publicized owing to confidentiality constraints. This does not, however, erode the deference owed FDA on its interpretation of its regulations or otherwise preclude FDA from maintaining a position that comports with the statute, FDA regulations, and long-standing Agency practice.

C. Allegations In Recent Lawsuit

In its complaint filed in D.C. District Court on September 25, 2012, Depomed seeks declaratory, injunctive, and other relief for FDA’s failure to recognize orphan exclusivity for Gralise on the date of Gralise’s approval, January 28, 2011. To the extent

the allegations in the complaint reiterate the legal arguments in the September 2011 letter, they are addressed above. Depomed also made new allegations not previously raised before the Agency. *See* Complaint ¶¶ 51-58. These allegations concern FDA's approval of Kogenate on February 25, 1993 and FDA's recognition of orphan exclusivity for Kogenate even though Kogenate was the same drug as a previously approved drug, Recombinate, that did not have orphan designation or exclusivity. FDA did not require a demonstration of clinical superiority in order for Kogenate to be awarded orphan-exclusive approval.

As described below, the 1993 grant of exclusivity for Kogenate was an outlier and erroneous decision reflecting an unusual agreement between the sponsors. Moreover, the Kogenate circumstances are not directly analogous to the circumstances here because the same drug had not been approved at the time of the Kogenate designation request. FDA is aware of at least five counter examples in which FDA *did require a plausible hypothesis of clinical superiority* in order for a drug to receive orphan designation when the drug was the same as one already approved that lacked orphan designation and exclusivity. These examples occurred in 1994, 2001, 2004, 2007, and 2012.³⁸ The sponsors in these examples ultimately failed to receive designation, but the examples are directly analogous to Gralise because FDA required the sponsors to offer a plausible hypothesis of clinical superiority in exactly the same circumstances that FDA did for Gralise.

Further, if any of these sponsors had ultimately received designation, FDA would not have granted orphan exclusivity unless they had also demonstrated clinical superiority upon approval, just as FDA has required for Gralise. FDA has identified at least nine instances in which drugs that have received orphan designation (based either on a presentation of a plausible hypothesis of clinical superiority or on the fact that the same drug had not yet been approved at the time of the designation request) were denied exclusivity when they have failed to demonstrate upon approval that they were in fact clinically superior to the previously approved drug. Contrary to Depomed's assertion, FDA is treating like products the same in requiring a clinical superiority hypothesis and then demonstration of superiority for Gralise to be eligible for orphan designation and exclusivity. Were FDA to depart from this practice, and not require clinical superiority for Gralise, it would be treating Depomed differently from how it has treated a significant number of similarly-situated sponsors.

The Kogenate example has several distinguishing features. Kogenate and Recombinate are both recombinant antihemophilic factors used to prevent and treat bleeding episodes in patients with hemophilia A; they are considered the same drug under orphan drug regulations. The Kogenate sponsor, Miles (later Bayer), sought and received orphan designation in 1989 before any such recombinant drug had been approved for the orphan indication in question (unlike the scenario here, where the Gralise sponsor sought designation more than four years after Neurontin had already been approved for the orphan indication at issue).³⁹ The Recombinate sponsor, Baxter, chose not to seek orphan

³⁸ FDA cannot disclose the details of these prior examples because of confidentiality constraints.

³⁹ *See supra* note 37.

designation for its drug. Both the Kogenate sponsor and the Recombinate sponsor submitted marketing applications and were uncertain about which product would be approved first. Presumably because of this uncertainty, the two sponsors reached a contractual agreement in which they agreed to share orphan exclusivity.⁴⁰ FDA supported this agreement at the time, in mid-1992 (prior to publishing the final rule,⁴¹ which took effect in early 1993) because this agreement to share Bayer's exclusivity encouraged the development and availability of two recombinant products instead of just one. Having two such products available was a particular priority because of concerns about potential viral transmission (*e.g.*, HIV viral transmission) associated with the existing plasma-derived products – concerns not associated with the two recombinant products under review. Further, FDA was anticipating the possibility of a shortage of recombinant products, which could be mitigated by having two recombinant products on the market instead of one (indeed, product shortage was the focus of the 1998 advisory committee meeting cited by Depomed).

To FDA's knowledge, the Kogenate example is an outlier that was influenced by the exigencies of the time and peculiar circumstances. Depomed tries to suggest otherwise – that this decision reflected a fundamentally different understanding of the Orphan Drug Act – by citing an excerpt from the 1998 advisory committee meeting on product shortage, in which a question arose about why Kogenate received orphan-exclusive approval despite being approved after Recombinate and not having demonstrated clinical superiority to Recombinate. *See* Complaint ¶ 57. Depomed cites this transcript excerpt out of context. Almost immediately following Depomed's selected excerpt, the same FDA presenter clarified that "The Baxter product, and [the] Bayer [product], are [both] on the market because of an agreement between the two companies. I believe that is public knowledge." Transcript of December 11, 1998, meeting of FDA Blood Products Advisory Committee, p. 108.⁴² At any rate, the statement that Depomed cites – the statement of one FDA official allegedly purporting to interpret the Orphan Drug Act in an advisory committee meeting addressing shortage of blood products – was informal communication that does not bind or otherwise obligate or commit the Agency to the views expressed. 21 CFR 10.85(k).

In short, FDA is treating Depomed in the same fashion that it has treated a number of similarly-situated sponsors in the last decade. Our decision is thus consistent with *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20 (D.D.C. 1997).

⁴⁰ FDA had previously rejected the idea of "shared" exclusivity under the statute "except where agreed to by the sponsor of the drug with the right to exclusive marketing." 56 Fed. Reg. 3338.

⁴¹ See Orphan Drug Regulations (final rule), 57 Fed. Reg. 62076 (Dec. 29, 1992).

⁴² In FDA's version of the public transcript, the excerpt that Depomed cites is on the page immediately prior to this one, page 107. (Depomed appears to be citing a differently paginated version of the transcript when it cites page 101, not page 107.)

V. Scientific Analysis: Gralise Is Not Eligible For Orphan Exclusivity Predicated On A Clinical Superiority Demonstration

Under Depomed's alternative exclusivity theory premised on clinical superiority, Depomed seeks a seven-year exclusivity period of a more limited scope vis-à-vis generic Gralise products (rather than all generic versions of both Neurontin and Gralise). A demonstration of clinical superiority for orphan exclusivity would require that Gralise be "shown to provide a significant therapeutic advantage over and above that provided by" Neurontin, whether in terms of greater effectiveness, greater safety, or a major contribution to patient care. 21 CFR 316.3(b)(3).

Following approval, Depomed contacted OOPD to inquire about exclusivity on the ground of clinical superiority. OOPD consulted with the Center for Drug Evaluation and Research (CDER), Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), as to whether the application for Gralise demonstrated clinical superiority over Neurontin in terms of greater safety. On February 9, 2011, OOPD notified the sponsor by phone that FDA had determined that the Gralise NDA had not included sufficient data and information to demonstrate that Gralise was clinically superior to Neurontin in terms of greater safety. The sponsor continued to make a case for the clinical superiority of Gralise through submissions to the Agency dated from early May 2011 through late September 2012. *See, e.g.*, September 2011 letter, pp. 15-28; April 2012 meeting; May 2012 submissions; July 2012 submission; August 2012 submission; September 25, 2012 submission.⁴³ FDA has evaluated the data and information submitted in support of the assertion that Gralise is clinically superior to Neurontin in terms of greater safety or, alternatively, by making a major contribution to patient care. For the reasons described below, FDA has determined that Gralise has not been shown to be clinically superior to Neurontin. Accordingly, Gralise is not eligible for orphan exclusivity predicated on clinical superiority.

A. Gralise Has Not Been Shown To Provide "Greater Safety In A Substantial Portion Of The Target Populations"

Clinical superiority in terms of greater safety, for the purpose of orphan exclusivity, is defined as "[g]reater safety in a substantial portion of the target populations." 21 CFR 316.3(b)(3)(ii). The sponsor argued that Gralise is associated with reduced incidence of adverse events (AEs) compared to Neurontin, in particular lower incidence of the three most common AEs for Neurontin – dizziness, somnolence, and peripheral edema – as evidenced by the AEs reported during the separate clinical trials supporting approval of Gralise and Neurontin, respectively. These studies each compared one drug, Neurontin or Gralise, to a placebo; no head-to-head trials were performed directly comparing Gralise to Neurontin. Although the sponsor concedes that "a direct comparison cannot be made" between the separate clinical trials for each drug, the sponsor maintains that the separate studies were "of similar size and nearly identical design." September 2011 letter, p. 15 (quoting an earlier Abbott submission for

⁴³ *See supra* note 1.

Gralise⁴⁴). Among the cross-study similarities you note in your September 2011 letter are similar patient populations, including age and sex, and similar duration of drug exposure despite higher maximum dosage in the Neurontin studies (1800 to 3600 mg/day versus 1800 mg/day in the Gralise studies). *Id.*, pp. 18-21. You state that: “Given these similarities in the Gralise and Neurontin studies, comparison of the incidence of adverse events in the studies is a valid method for demonstrating clinical superiority of Gralise over Neurontin with regard to safety.” *Id.*, p. 22. Using various methodologies described in the September 2011 letter (pp. 22-27), the sponsor compared the AEs across the different studies and estimated various degrees of difference between the Neurontin and Gralise AEs. One comparison methodology, which controlled for dosage of gabapentin at 1800 mg/day, yielded the following differences for the three most common AEs associated with Neurontin: 28.7% of patients experienced dizziness on Neurontin versus 10.9% on Gralise; 17.4% of patients experienced somnolence on Neurontin versus 4.5% on Gralise; and 7.0% experienced diarrhea on Neurontin versus 3.3% on Gralise. *Id.*, p. 27.

FDA disagrees with your methodology for comparing the AEs in this instance. Cross-study comparisons are generally of only limited utility for a variety of reasons, including: differences in clinical practice and clinical conditions in which the studies are conducted (*e.g.*, if the studies are several years or more apart, as occurred here); differences in how AEs are reported and documented (*e.g.*, self-reported or solicited, at what intervals, whether classification by severity was left to the investigator’s discretion or delineated in the protocol); differences in methodologies for compiling and analyzing AEs; and the possibility that there will be differences in the incidence of AEs based on chance alone, regardless of study design. In addition to these general infirmities, in this instance the AE profiles for Neurontin and Gralise are quite similar in terms of specific types and seriousness of AEs, differing only in proportions of study subjects experiencing the AEs. Further infirmity in this cross-study comparison stems from the fact that the AEs were for the most part patient-reported outcomes, such as dizziness, nausea, and somnolence, rather than objective outcomes that can be measured by an observer. For all of these reasons, Depomed’s cross-study comparison does not provide persuasive evidence to show that Gralise is clinically superior to Neurontin regarding safety.

FDA acknowledges that the pharmacokinetic (PK) profiles of the two products are different, as illustrated in the graph included in your July 2012 submission (p. 5). Depomed attributes the purported reduction in AEs to this difference – to the fact that Gralise’s once-daily evening dosing achieves a single, extended peak of the drug throughout the late evening and early morning hours, whereas Neurontin’s three-times daily dosing achieves multiple peaks of the drug during the day. July 2012 submission, p. 5. As described above, FDA does not agree that the AEs for Gralise have been shown to be meaningfully lower than the AEs for Neurontin. In addition, although the PK profiles for the two products are different, it is unclear whether and how these PK profiles influence safety. The pharmacokinetic/pharmacodynamic (PK/PD) relationship for the AEs for gabapentin has not been defined. Although it is theoretically possible that the different PK profile for Gralise results in greater safety compared to Neurontin, this

⁴⁴ See *supra* note 10.

theory assumes that the AEs resulting from gabapentin administration are related to the peak plasma concentrations of gabapentin, which has not been demonstrated.

For the reasons described above, FDA has determined that the cross-study comparison does not demonstrate that Gralise provides a significant therapeutic advantage over Neurontin in terms of safety. FDA acknowledges that the orphan drug regulations state that direct comparative trials would be required in only “some cases” to support greater safety showings, as compared to in “most cases” for greater effectiveness showings. *Compare id. with* 21 CFR 316.3(b)(3)(i). FDA has nonetheless determined that, in the absence of more convincing data than Depomed has been able to produce to date, this greater safety showing for Gralise would require head-to-head trials given the overall similarity in type and seriousness of AEs, their patient-reported nature, and the undefined PK/PD relationship for AEs for these drug products.

In the past, FDA has accepted diminution in AEs as manifested in cross-study comparisons as evidence of clinical superiority in terms of greater safety for other (non-analgesic) drug products. Two examples of such regulatory decisions, which you cite in your September 2011 letter (p. 17), involved Avonex versus Betaseron (interferon beta-1a) and AmBisome versus Abelcet (amphotericin B). In both prior cases, the AEs were objective endpoints that could be measured by an observer – skin necrosis and injection site reactions for Avonex, and infusion-related reactions for AmBisome – unlike the largely patient-reported outcomes for Gralise and Neurontin. Additional distinguishing features were the seriousness of the AEs for Avonex and Ambisome, as well as the degree of difference in reported AEs between these two drugs and their respective comparators. *See Berlex Labs. v. FDA*, 942 F. Supp. 19, 23-24 (D.D.C. 1996) (“The substantial disparity between Avonex and Betaseron with regard to injection site necrosis was surely a factor relevant to safety, and Berlex [manufacturer of Betaseron] does not challenge the sufficiency of the record evidence on that point. FDA had an adequate basis upon which to consider Avonex ‘clinically superior’ to Betaseron.”).

Other Agency decisions that you cite as “regulatory precedent” are likewise inapposite. FDA has previously found products to be clinically superior in terms of safety, for the purpose of orphan exclusivity, without requiring evidence from direct comparative trials when the drug products at issue eliminated an ingredient or contaminant known to be associated with a relatively frequent adverse event or when the manufacturing process yielded a superior safety margin. Two examples of such regulatory decisions, which you cite in your September 2011 letter (p. 17), were: comparing Mononine versus AlphaNine (coagulation factor IX (human)), based on a difference in the manufacturing process relevant to the risk of Hepatitis C transmission; and comparing BeneFix (coagulation factor IX (recombinant)) versus Mononine and Alphanine (coagulation factor IX (human)), based on the former being recombinant rather than human-derived and hence inherently safer regarding person-to-person transmission of infectious agents.⁴⁵ In these examples, an inherent difference between

⁴⁵ Plasma-derived products carry a risk of viral transmission due to inclusion of human components. Recombinant products are formulated without the use of any human components, so there is believed to be no risk of passing any pathogen found in human blood.

the products conveyed a significant therapeutic advantage in terms of safety. By contrast, the inherent difference between Gralise and Neurontin – the differing PK profile as a result of Gralise’s once-a-day formulation versus Neurontin’s three daily doses – has not been shown to convey any such therapeutic advantage. As described above, the PK/PD relationship for the AEs for gabapentin has not been defined; Depomed has not demonstrated that Gralise’s PK profile, as compared to Neurontin’s, leads to greater safety in a substantial portion of the target population.

B. Gralise Has Not Been Shown To Provide A “Major Contribution to Patient Care”

FDA regulations provide that, “[i]n unusual cases, where neither greater safety nor greater effectiveness has been shown,” a drug may be considered “clinically superior” for the purpose of orphan exclusivity through “a demonstration that the drug otherwise makes a major contribution to patient care.” 21 CFR 316.3(b)(3)(iii). Major contribution to patient care is intended to capture only significant improvements, not minor conveniences or otherwise insignificant changes. *See* CFR 316.3(b)(3) (defining “clinically superior” as having “shown to provide a *significant therapeutic advantage* over and above that provided by” an already approved drug) (emphasis added). Since first proposing the orphan drug regulations in 1991, FDA has stated that major contribution to patient care represents a “narrow category . . . not intended to open the flood gates . . . for every drug for which a minor convenience over and above that attributed to an already approved drug can be demonstrated.” 56 Fed. Reg. 3343. Indeed, the regulation itself makes clear that the category is restrictive, with the phrase “[i]n unusual cases.” 21 CFR 316.3(b)(3)(iii). An example that FDA has proffered in the past of a “major contribution to patient care” is an oral dosage form for a drug that was previously available only in a parenteral dosage form. 56 Fed. Reg. 3343. FDA has further stated that any determination of major contribution to patient care is to be made on a case-by-case basis, taking into account the nature of the specific disease or condition, the nature of the specific drug, the nature of the mode of administration, and other factors. 57 Fed. Reg. 62079.

The sponsor presented its case for Gralise making a major contribution to patient care in its submissions to the Agency dated from early May through late September 2012. According to the sponsor, a “global assessment” of the following factors leads to a finding of major contribution to patient care:

1. Greater safety of Gralise, as demonstrated by “significant reductions in the most frequent and material adverse events” when compared to Neurontin;
2. “[A]n enhanced ability to titrate patients to the optimal effective dose” because of this purported reduction in AEs;
3. “[F]ewer patients switching to other therapies or adding therapies (often opioids),” again because of the purported reduction in AEs;
4. Greater convenience in once-a-day dosing, which “leads to better compliance”; and

5. “[E]nhanced relief of nighttime pain” owing to Gralise’s evening dosing schedule and PK profile. July 2012 submission, pp. 2-3.

FDA has evaluated these reasons individually and cumulatively and has determined that Gralise has not been shown to provide a major contribution to patient care.

1. Greater Safety

The sponsor maintains that Gralise has fewer AEs than Neurontin, based on a comparison of the safety data in the product labels for each drug. In particular, the sponsor points to a reduction in somnolence and dizziness as leading to fewer falls among the geriatric population. *See* July 2012 submission, p. 7. As described in detail in Section V.A, above, FDA has determined that the sponsor’s cross-study comparison of AEs does not demonstrate that the AEs for Gralise are meaningfully lower than the AEs for Neurontin. In particular, the sponsor has not demonstrated that Gralise carries a reduced incidence of dizziness and somnolence that results in a reduced risk of falls among the elderly patients who constitute the majority of PHN patients.⁴⁶

2. Enhanced Ability To Titrate To Optimal Effective Dose

The sponsor also maintains that Gralise provides an enhanced ability to titrate patients to the optimal effective dose of at least 1800 mg/day because there are fewer AEs. As support, the sponsor offers the purported reduction in AEs coupled with claims data and internal script volume data.⁴⁷ According to these claims data, less than 15% of patients prescribed gabapentin TID were titrated to the optimal dose of at least 1800 mg/day.⁴⁸ Further, the mean maximum dose, which was defined as the highest observed daily dosage for at least 14 consecutive days, was only 970 mg.⁴⁹ In contrast, the sponsor points to internal script volume data from the first 8 months following the Gralise launch, which indicates that over 61% of the Gralise prescriptions were for at least 1800 mg/day, with an average daily dose of 1371 mg. July 2012 submission, p. 7.

FDA finds the reduction in AEs unconvincing, as already discussed. These claims data and internal script volume data are likewise unpersuasive. The data collected for gabapentin TID was for a significantly longer period of time than the data collected for Gralise (*i.e.*, greater than four years versus eight months). Based on the limited data collected for Gralise, it is unclear whether the Gralise population would be able to sustain this higher dosage for long periods of time. Even assuming the sponsor could show that

⁴⁶ The sponsor cites articles from Hausdorff *et al.*, Hornbrook *et al.*, and Sterling *et al.* (references 6, 7 and 9 in July 2012 submission) to augment the claim that the elderly population is at an increased risk of falling and suffering injury from falls compared to the general population. Even assuming that the elderly population has this increased risk, the sponsor has not provided data to show that the use of Gralise, as compared to gabapentin TID, decreases the risk of falls and associated injuries in the elderly.

⁴⁷ These internal script volume data do not appear to be validated.

⁴⁸ The claims data were described in two poster presentations by Johnson *et al.*, one at the May 2012 American Pain Society Annual Meeting and one at the February 2012 Conference of the American Academy of Pain Medicine.

⁴⁹ With a reported standard deviation of 738 mg.

the average daily dose of Gralise remains higher than gabapentin TID over a prolonged period, this feature would not rise to the level of providing a “significant therapeutic advantage” over Neurontin, at least not without also showing that this higher dose results in fewer AEs or that it achieves greater pain control. 21 CFR 316.3(b)(3).

3. Fewer Patients Switching Or Adding Therapies

The sponsor contends that fewer patients who are treated with Gralise, as compared to Neurontin, either switch therapies or add therapies (*i.e.*, opioids). As support, the sponsor again relies on the claimed reduction in AEs for Gralise, and notes that dizziness and somnolence AEs were cited as the primary reasons for discontinuing both Neurontin and Gralise. The sponsor also relies on the claims data and internal script volume data described above. The claims data, according to the sponsor, indicate that 57.9% of patients prescribed gabapentin TID switched therapy, while 37% added a therapy (adding opioids more than half of the time) from June 2005 to February 2010.⁵⁰ The internal script volume data purportedly show that over 61% of the Gralise prescriptions were for at least 1800 mg/day (*i.e.*, at or above therapeutic levels) eight months after the launch of Gralise. The sponsor presents these internal data presumably to suggest that the Gralise patients did not add other therapies. *See* May 2102 submissions.

FDA does not agree that these data and information demonstrate that fewer patients on Gralise switch or add therapies. As noted, the cross-study comparison of AEs does not demonstrate that Gralise is associated with a reduced incidence of AEs as compared to Neurontin. The claims data do not address why patients discontinued the gabapentin TID or whether the discontinuation was due to AEs. The sponsor also did not provide any data on the number of patients who discontinued Gralise; without this data, it is impossible to compare these two groups for this factor. Lastly, as noted earlier, the claims data evaluating gabapentin TID spanned more than four years, whereas the internal script volume data for Gralise were generated for only eight months. This difference in time periods is likely to result in an increased statistical probability for there to be reports of switching and/or supplementing therapies with gabapentin TID.

4. Increased Convenience And Compliance

The sponsor states that the once-a-day dosing of Gralise provides greater convenience and leads to improved patient compliance when compared to Neurontin. The sponsor cites an article by Saini *et al.* (reference 14 in July 2012 submission) that indicates that, among patients with chronic diseases with long quiescent phases, there is a 22% to 41% increase in adherent days for once-a-day dosed patients as compared to the thrice-a-day dosed patients.

⁵⁰ Data is from a poster presentation by Johnson *et al.* at the May 2012 American Pain Society Annual Meeting.

FDA finds this article unpersuasive. The dosing regimens reviewed in the article were for chronic diseases that, unlike PHN, were quiescent (*i.e.*, maintenance therapy). The sponsor did not provide any data that extrapolates the compliance rate for maintenance therapy to therapy for an active painful condition such as PHN. One could reasonably expect a person with an active painful condition to be more compliant with a medical regimen than a person with an asymptomatic chronic condition. This article therefore does not demonstrate that patients on Gralise, with its once-a-day dosing, will be more compliant than patients on gabapentin TID. To the extent that once-a-day dosing may be more convenient than thrice-daily dosing, FDA has never accepted “minor convenience” as evidence that a drug provides a major contribution to patient care. *See* 56 Fed. Reg. 3343 (describing “major contribution to patient care” as a “narrow category . . . not intended to open the flood gates . . . for every drug for which a minor convenience over and above that attributed to an already approved drug can be demonstrated”).

5. Enhanced Nighttime Pain Relief

Lastly, the sponsor states that Gralise’s nocturnal dosing enhances nighttime pain relief because of the drug’s PK profile, which shows higher nocturnal plasma concentrations of Gralise than gabapentin TID. The sponsor references a study by Odrich *et al.* that documents increased nocturnal pain in patients suffering from chronic neuropathic pain, including patients with PHN. *See* July 2012 submission, p. 5 and ref. 15. The sponsor also provides results of an Awareness, Trial and Usage (ATU) survey conducted among 275 physicians, in which 49% of physicians agreed that Gralise provides meaningful nocturnal pain relief as compared to 23% for gabapentin TID. *See* August 2012 submission.

FDA finds the sponsor’s evidence unpersuasive. First, although the PK profiles for the two products are different, it is unclear whether and how these PK profiles influence pain relief; the sponsor has not provided any data to relate the higher nocturnal blood levels of gabapentin to improved pain control. Although it may appear that higher blood levels of gabapentin could produce improved pain control, no data were provided to identify relevant saturation levels for this treatment. Second, although the survey could have provided association between increased blood levels of Gralise and pain control had it represented patient response to Gralise or physician experience prescribing Gralise, the survey did neither. The survey does not reflect the physicians’ actual experience with Gralise: only 2% of the 275 physicians surveyed had ever prescribed Gralise. The survey instead reflects physicians’ perception of Gralise after reading the Gralise labeling and comparing it to the Neurontin labeling. Because the survey did not evaluate the product based on actual usage, it is inadequate to demonstrate that Gralise provides a “significant therapeutic advantage” over Neurontin. 21 CFR 316.3(b)(3). Another weakness in the study is that the physician sample is not a random sample but instead appears to be a sample of convenience.⁵¹

⁵¹ Inferences drawn from a convenience sample (*i.e.*, a sample selected based on easy access/availability rather than chosen in such a way as to be representative of the target population) are rarely generalizable to the target population and may not be valid.

6. Cumulative Assessment

FDA has articulated why each of the factors identified by the sponsor individually fails to demonstrate that Gralise provides a major contribution to patient care. FDA has also assessed these factors cumulatively, as the sponsor requested. In this cumulative assessment, FDA has considered all factors that are sufficiently supported by data or information. As noted above, FDA has evidentiary concerns with each of the factors identified by the sponsor except for the minor convenience of once-daily dosing instead of thrice-daily dosing. Even if FDA also accepted the contention that Gralise has an average higher daily dose compared to gabapentin TID, this factor is likewise not significant absent information showing that this higher dose is due to fewer AEs and/or achieves greater pain control. These two minor features combined do not rise to the level of demonstrating that Gralise provides “a significant therapeutic advantage” over Neurontin through providing a major contribution to patient care. 21 CFR 316.3(b)(3).

What the sponsor has not provided to assist with this cumulative assessment – despite a number of requests from FDA – is information that correlates the PK data (the high plasma levels of gabapentin at night) to clinical effect (*e.g.*, nighttime pain control, fewer AEs leading fewer falls, etc.). This information, if provided, may help bolster many of the theories proffered by the sponsor, including enhanced nighttime pain relief and lower risk of injury. The ATU survey could perhaps have made the connection if it were a random sampling of patients and/or physicians who were surveyed on their actual experiences with Gralise (instead of labeling comprehension). Even now, if the sponsor were able to correlate plasma levels with the occurrence of AEs or the elevated plasma levels with greater pain control, FDA would take such information into consideration in re-assessing major contribution to patient care.

In sum, FDA has determined that, based on the information provided by the sponsor to date, Gralise is not eligible for orphan exclusivity predicated on major contribution to patient care.


VI. CONCLUSION

For the reasons described above, we reaffirm our initial conclusion that Gralise is not entitled to orphan-drug exclusivity under the Orphan Drug Act and FDA regulations absent a demonstration of clinical superiority, because it is the same drug as a drug already approved for the same use, Neurontin (and multiple approved generic versions of Neurontin). We further conclude that Gralise has not been demonstrated to be clinically superior to Neurontin, whether in terms of greater safety or by making a major contribution to patient care. Gralise is thus ineligible for orphan-drug exclusivity. This decision is consistent with the governing statute, implementing regulations, and Agency practice, and best effectuates the important aim of the Orphan Drug Act.

Gralise will continue to enjoy its three years of market exclusivity vis-à-vis potential generic competitors under section 505 (21 U.S.C. § 355), for conducting one

clinical investigation considered essential to and supporting approval of its new formulation of gabapentin. Depomed is not, however, entitled to a seven-year period of exclusivity vis-à-vis all gabapentin products indicated for this orphan indication.

Sincerely,



Gayatri R. Rao, M.D., J.D.

Director

Office of Orphan Products Development

cc:

Elizabeth Dickinson, Esq.
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Office of the Chief Counsel, FDA
White Oak Bldg. 31, Rm. 4536
10903 New Hampshire
Silver Spring, MD 20993
elizabeth.dickinson@fda.hhs.gov

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Hayley Welton, RAC
Director, Regulatory Affairs
Depomed, Inc.
1360 O'Brien Drive
Menlo Park, CA 94025
hwelton@depomedinc.com

EXHIBIT 13

Review of Request for Orphan Designation

Designation Number:

Date Received by FDA: June 2, 1998
Date Received by Reviewer: June 3, 1998
Date Review Started: September 28, 1998
Date Review Completed: April 27, 1999

Product:

Trade Name: ProLease® rhGH
Generic Name: Sustained-release Recombinant human growth hormone
Somatotropin (rDNA origin)

Sponsor:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Manufacturer:

Not given

Contact Person:

Robert L. Garnick, Ph.D.
Vice President, Regulatory Affairs
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
Phone: 650-225-1202

Regulatory Status:

Alkermes, Inc. holds _____ / for ProLease rhGH. _____ to
Alkermes to produce the final ProLease formulation.

_____. In addition, other marketed rhGH products in the
United States include Humatrope®, Genotropin®, Norditropin®, and Saizen®. Protropin® is an
approved methionyl growth hormone product. (See Table 1). The sponsor plans on submitting an
NDA for this product in approximately June, 1999.

Indication: Long-term treatment of children who have growth failure due to lack of adequate
endogenous growth hormone secretion.

Disease/Condition Background Information:

Idiopathic growth hormone deficiency is defined as a condition in which the amount of growth
hormone released by the pituitary is insufficient to support normal growth in children. The
diagnosis of classic growth hormone deficiency is suspected when heights are more than three
standard deviations below the mean for age and gender.

- a) Growth velocity less than 4.5cm/yr or less than 10th centile for age;
- b) Bone age greater than 2 yrs delayed or 2 SD below the mean for patients 5 yrs old and older; bone age greater than 1 yr delayed or 1 SD below the mean for patients younger than 5 yrs old;
- c) Height greater than 3 SD below the mean; and
- d) Growth hormone response to 2 provocative tests of less than 8.0ng/ml (tests include: arginine, insulin, L-dopa, clonidine, glucagon).

Organic growth hormone deficiency is also defined as a lack of sufficient growth hormone to support normal growth. However, the deficiency is caused by a lesion affecting the hypothalamus or pituitary which may be either acquired or congenital. The same criteria, as outlined above, is used to determine organic growth hormone deficiency as for idiopathic growth hormone deficiency except that the bone age and height may not be delayed in cases of relatively new organic dysfunction.

Growth hormone releasing hormone is produced in the hypothalamus and transported by the hypophyseal-portal system to the pituitary gland. After it attaches to the appropriate receptor sites on the somatotroph, growth hormone is synthesized. The newly synthesized hormone is released into the circulation, and produces all of its known actions, especially the production of somatomedin-C. Somatomedin-C binds to cellular receptors, stimulating the events necessary for linear growth. Endogenous GH release is modulated by somatostatin, GH and somatomedin-C, all involving feedback mechanisms. This feedback inhibition, especially by somatostatin, is probably responsible for the pulsatile manner in which GH is released.

Treatment of children with classic growth hormone deficiency is started as early as possible with human growth hormone 0.18-0.3 mg/kg per week, given in six or seven divided doses. Eli Lilly's brand of somatotropin is the only preparation that is labeled for three times a week administration. Therapy is continued until there is no more response, which generally coincides with epiphyseal closure. Maximal response occurs in the first year of treatment.

Population Estimate:

Estimates of the prevalence rate of pediatric growth hormone deficiency range from 20.1¹ to 28.7 per 100,000. Applying these rates to the United States population of 0-18 year olds results in estimates of prevalence between 12,800 and 18,300. For purposes of this designation, the prevalence of children who have growth failure due to lack of adequate endogenous growth hormone secretion is 18,000.

Rationale for Use:

Several products are approved for pediatric growth hormone deficiency and are included in Table 1. This application makes the case that this formulation presents a novel sustained release formulation of somatotropin, thus qualifying as a "major contribution to patient care" under

21 CFR 316.3(b)(3)(iii) of the Orphan Drug regulations. The sponsor makes the argument that once-a-month or twice-a-month therapy is a major contribution to patient care, when compared to the typical once daily to three times a week subcutaneous injections or intramuscular injections.

Genentech sponsored a multicenter, open-label, randomized trial comparing Prolease® rhGH in children with growth failure due to growth hormone deficiency. Seventy-four patients were randomized to receive either 1.5 mg/kg ProLease® given once a month or 0.75 mg/kg ProLease® given twice a month. The primary endpoint was the six-month annualized growth rate. Secondary endpoints were standardized height and bone age at six months, using the Fels Institute method.

Of the 74 patients enrolled, 69 completed the study. Only 53 had pre-study growth rates available. The six-month annualized growth rate for the 1.5 mg/kg group was 8.5 cm/year \pm 1.7 cm/year compared to the pre-study growth rate of 5.0 cm/year \pm 2.1 cm/year (n=25). (P<0.0001). For the 0.75 mg/kg (twice monthly) group, the six-month annualized growth rate was similar at 8.6 cm/year \pm 2.4 cm/year compared to the pre-study growth rate of 4.6 cm/year \pm 1.8 cm/year (n=28). The standardized height changed from -3.0 (\pm 1.2) and -3.0 (\pm 0.7) standard deviations at baseline in the 1.5 mg/kg group and 0.75 mg/kg twice monthly group, respectively, to -2.6 standard deviations in each group at six months (p<0.0001 in both groups). No group in this trial was given daily or three times per week dosing of rhHG. Therefore, comparisons of efficacy to once monthly or twice monthly dosage forms cannot be determined from this trial.

Evaluation and Recommendation:

Genentech, Inc. has applied for the treatment of growth hormone deficiency in children with Prolease®, a sustained release recombinant growth hormone product. The sponsor makes that argument that the once or twice monthly dosing of Prolease® compared to once daily dosing of other somatropin products represents an increase in convenience by less frequent dosing and therefore, a major contribution to patient care according to 21 CFR 316.3(b)(3)(iii). There are several human growth hormone products that are presently approved for the indication sought for in this application. All of these, with the exception of Eli Lilly's Humatrope® and Serono's Saizen®, are labeled for daily administration. Humatrope® is labeled for either three or six times a week administration. Saizen® is labeled for three times weekly administrations.

Where no increased safety or efficacy has been demonstrated, a product can still be determined to be clinically superior in the unusual case "that the drug otherwise makes a major contribution to patient care".² The determination of that what constitutes a major contribution to patient care has been on a case-by-case basis which is reflected in the preamble to the Orphan Drug Regulations. The only precedent to-date for a major contribution to patient care is the case of Sandostatin LAR when compared to Sandostatin. This determination was based on a once monthly injection being a major contribution to patient care when compared to three times daily injections.

The argument in this application is less clear, comparing once or twice monthly injections to daily injections and/or three times a week injections. It is acknowledged that a change from a three times a week injection to an every two week injection would constitute a contribution to patient care occurs. However, it is this reviewer's opinion that this does not constitute a major contribution to patient care as specified under the Orphan Drug Act. Therefore, it is recommended that the sponsor's application for orphan designation be denied.



Michael W. Dreis, Pharm.D., M.P.H.

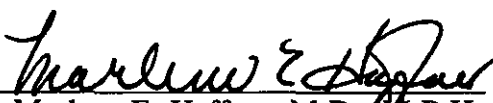
Concur:  Date: 5/10/99
Marlene E. Haffner, M.D., M.P.H.

Table 1
FDA Approved Human Growth Hormone

Generic/Brand	Company	Indication	Dose and schedule	Route
Somatrem (Protropin®)	Genentech	In children due to lack of adequate endogenous growth hormone secretion	0.3 mg/kg/week administered daily	IM or SC
Somatropin (Nutropin®) Freeze-dried formulation	Genentech	In children due to lack of adequate endogenous growth hormone secretion PLUS indication in renal transplants PLUS short stature associated with Turner's Syndrome	0.3 mg/kg/week administered daily	SC
Somatropin (Nutropin AQ®) Liquid formulation	Genentech	In children due to lack of adequate endogenous growth hormone secretion PLUS indication in renal transplants	0.3 mg/kg/week administered daily	SC
Somatropin (Humatrope®)	Lilly	In children due to lack of adequate endogenous growth hormone secretion PLUS short stature associated with Turner's Syndrome	0.18 mg/kg/week given on three alternate days or 6 times/week	IM or SC
Somatropin (Genotropin®)	Pharmacia & Upjohn	In children due to lack of adequate endogenous growth hormone secretion	0.16 - 0.24 mg/kg/ week in 6 to 7 doses	SC
Somatotropin (Norditropin®)	Novo Nordisk	In children due to lack of adequate endogenous growth hormone secretion	0.024 – 0.034 mg/kg 6 to 7 times/week	SC
Somatotropin (Saizen®)	Serono	In children due to lack of adequate endogenous growth hormone secretion	0.06 mg/kg (0.18 IU/kg) three times weekly	SC or IM

References

¹ Lindsay R, Feldkamp M, Harris D et al. Utah growth study: growth standards and the prevalence of growth hormone deficiency. *J Pediatr* 1994;125:29-35.

² Orphan Drug Regulations. *Federal Register* Dec. 29, 1992; 57 FR 62076.

EXHIBIT 14

LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

FILE COPY

FRANK J. SASINOWSKI

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Direct Dial (202) 737-4287

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FACSIMILE
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July 20, 2009

BY E-MAIL AND COURIER

Timothy Coté, M.D., M.P.H.
Director
Office of Orphan Products Development
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RECEIVED
JUL 20 2009
OFFICE OF ORPHAN
PRODUCTS DEVELOPMENT

RE: Orphan Drug Designation Request No. 04-1891 – Inhaled Treprostinil Sodium for Pulmonary Arterial Hypertension

Dear Dr. Coté:

In preparation for our meeting tentatively scheduled for July 28, 2009, and on behalf of our client, United Therapeutics Corporation (“UTC”), we are providing you with the enclosed briefing materials concerning the above-referenced Orphan Drug Designation Request. The purpose of the meeting is to discuss the Office of Orphan Products Development’s (“OOPD’s”) May 5, 2009 letter (Exhibit #1) in which the Office raised issues concerning UTC’s request for designation of Inhaled Treprostinil Sodium (“INH TRE”) for the treatment of patients with Pulmonary Arterial Hypertension (“PAH”) with NYHA functional Class II-IV symptoms. OOPD concluded in that letter that the clinical superiority arguments in relation to the Subcutaneous (“SC”) and Intravenous (“IV”) versions of TRE (i.e., greater safety and major contribution to patient care) that UTC raised in its March 16, 2009 amendment (Exhibit #2) did not warrant orphan drug designation at that time.

While we advance no further information or arguments on the major contribution to patient care aspect at this time, the focus of this submission and our meeting is with respect to clinical superiority based on greater safety of INH TRE over SC TRE and over IV TRE. With respect to the question of whether INH TRE is superior on safety grounds to SC TRE, OOPD stated in its May 5, 2009 letter the following:

4819 EMPEROR BOULEVARD
SUITE 400
DURHAM, NORTH CAROLINA 27703
(919) 313-4750
FAX (919) 313-4751

FDA 0990

Timothy Coté, M.D., M.P.H.
July 20, 2009
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HYMAN, PHELPS & MCNAMARA, P.C.

In your March 16, 2009, amendment you make the claim that treprostinil of inhalation is safer than the approved subcutaneous formulation of the drug. A drug administered as an inhalation obviously avoids any possible injection site pain because of its route of administration. However, this does not mean that the inhalation route of administration is without risks. We consulted with the medical officer in the [Division of Cardiovascular and Renal Products (“Review Division”)] who is reviewing the NDA for treprostinil for inhalation. He noted several types of respiratory adverse events that were of concern, such as nasopharyngeal irritation, cough, and pulmonary bleeds. Therefore, it would appear that treprostinil for inhalation has its own unique adverse event profile. For purposes of orphan-designation, a safety advantage of one product over another should be unambiguous and well-defined. We do not believe that the safety profile of treprostinil for inhalation compared to the safety profile of subcutaneous treprostinil is significant enough to warrant orphan-drug designation.

While the above states specific concerns regarding the relative safety advantages of INH TRE compared to SC TRE, there are no specific grounds stated in OOPD’s May 5, 2009 letter for not finding that INH TRE is superior on safety grounds to IV TRE, other than the general need referenced above to show an “unambiguous”, “well-defined” and “significant enough” safety advantage. UTC stated in its March 16, 2009 amendment that the IV route is associated with the risk of catheter-related Blood Stream Infections (“BSIs”) and sepsis, which can be fatal, whereas with the inhalation route of administration there are no comparably serious risks. From an informal communication, we understand that the Office might not consider INH TRE clinically superior to IV TRE based on greater safety because OOPD may consider the risk of BSIs and sepsis to be the same for IV TRE as for any IV infusion drug product.

UTC has provided FDA’s Review Division with additional information concerning the “respiratory adverse events” noted in your May 5, 2009 letter. UTC believes that this information supports orphan designation of INH TRE, in that it shows that the safety advantage of INH TRE over SC TRE is unambiguous and well-defined and significant enough to warrant designation – particularly in light of and when compared to OOPD’s precedential superior safety clinical superiority decisions. Also, our additional research

Timothy Coté, M.D., M.P.H.
July 20, 2009
Page 3

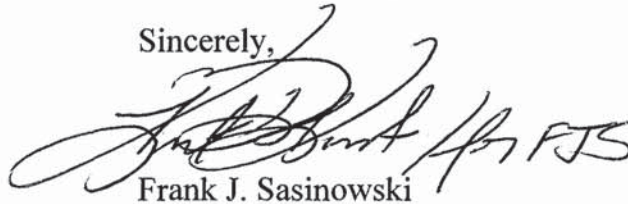
HYMAN, PHELPS & MCNAMARA, P.C.

shows that the labeled risk of sepsis with IV TRE stands out among IV drug products and that the safety advantage of INH TRE over IV TRE is also unambiguous and well-defined and significant enough to warrant designation. Annex I to this document discusses the information supporting designation of INH TRE as superior to the SC and IV versions of TRE. Annex II discusses OOPD's previous superior safety clinical superiority decisions as they relate to UTC's pending designation request.

###

We appreciate OOPD's consideration of this additional information demonstrating that INH TRE is not the "same drug" as the SC and IV versions of TRE for orphan designation purposes, because it is clinically superior, and look forward to meeting with you later this month (if OOPD determines that, after reviewing this new information and analyses, that a meeting is necessary because absent further discussion, a decision to recognize a designation in this case would not be forthcoming). Please contact me (202.737.4287) or my colleague, Kurt Karst (202.737.7544), if you have any questions or need any additional information.

Sincerely,

A handwritten signature in black ink, appearing to read "Frank J. Sasinowski", with a stylized flourish at the end.

Frank J. Sasinowski

FJS/KRK/eam

Enclosures

cc: Jeffrey Fritsch, R.Ph.
OOPD, FDA
Dean Bunce, EVP, Regulatory Affairs and Compliance
United Therapeutics Corporation

EXHIBIT 15



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203496

NDA APPROVAL

United Therapeutics Corporation
Attention: Dean Bunce, RAC
Executive Vice President,
Regulatory Affairs and Compliance
55T. W. Alexander Drive
P.O. Box 14186
Research Triangle Park, NC 27709

Dear Mr. Bunce:

Please refer to your New Drug Application (NDA) dated December 23, 2011, received December 27, 2011, resubmitted January 31 and August 16, 2013, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Orenitram (Treprostinil) Extended Release Tablets, 0.125 mg, 0.25 mg, 1mg, and 2.5 mg.

We acknowledge receipt of your amendments dated August 16, 20, September 13, October 8, 29, November 27, and December 18, 2013.

The August 16, 2013, submission constituted a complete response to our March 22, 2013, action letter.

This new drug application provides for the use of Orenitram (Treprostinil) Extended Release Tablets, 0.125 mg, 0.25 mg, 1mg, and 2.5 mg for treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your October 29, 2013, submission containing final printed carton and container labels.

Please submit final printed carton and immediate container labels that are identical to the carton and immediate container labels submitted on October 29, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 203496.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA

2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Wayne Amchin, Regulatory Project Manager, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal
Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
12/20/2013

EXHIBIT 16

November 15, 1993

FILE COPY

RECEIVED

NOV 17 1993

Application #93-752

Office of Orphan Products Development

Dear Dr. Haffner,

Thank you for your letter of August 20 requesting further information prior to your designation of buprenorphine as an orphan drug.

As outlined in section 8 of our application, the number of potential patients who may actually be available for treatment with buprenorphine is likely to be substantially less than the 115,000 individuals who could be enrolled in methadone treatment programs.

The specific pharmacological characteristic of buprenorphine which may limit its use in the addict population is its partial agonist activity at the μ receptor compared to the full μ agonist activity of morphine, methadone and LAAM. Those addicts who are tolerant to high levels of μ agonism are unlikely to be adequately maintained at even the highest doses of buprenorphine. While the blind has not yet been broken in the ongoing multi-center trials, the drop-out rate from those trials would seem to confirm our expectations that individuals who are tolerant to high levels of opiates will not be sufficiently maintained on buprenorphine. (see #3 below).

We believe that the patient population suitable for treatment with buprenorphine for narcotic addiction is substantially below the 200,000 limit currently established. Additionally, the economics of marketing buprenorphine and buprenorphine/naloxone for this indication are such that we do not anticipate that sales of buprenorphine in the United States will be adequate to recover the preclinical and clinical development costs within seven years of approval.

Included with this letter is a spreadsheet which outlines our expectation that the economics of marketing buprenorphine, either as a mono-substance or in combination with naloxone for this indication are such that we do not anticipate a profit from the product during the first seven years of marketing. As you are aware, we have reached an agreement with NIH/NIDA to proceed with a Cooperative Research and Development Agreement to develop buprenorphine and buprenorphine/naloxone for this indication, and have jointly established a decision point in the CRADA regarding Orphan Designation. Without the market protection afforded by Orphan Status it is unlikely that we could proceed with the cooperative development.

The attached spreadsheet has been prepared by our finance department and verified by our outside accounting firm, (b) (4). This information should be considered confidential.

In developing the spreadsheet, we've made the following determinations and assumptions:

1. The current maximum population eligible for treatment of addiction with any narcotic is limited to 115,000 patients (Methadone Treatment Slots). This limitation and the regulations establishing it are highly unlikely to be modified during the life of the product.
2. The current available patient population eligible for treatment with any narcotic is 104,000. This is the current number of patients enrolled in methadone treatment programs. This number differs from the maximum population because typically $\pm 10\%$ of available slots are unfilled at any given point. This figure is derived from the Federal Register Notice of July 20, 1993 page 38704. FDA Docket No. 93N-0040.
3. Buprenorphine is a partial agonist, as compared to methadone and LAAM which are both full agonists at the μ opiate receptor. Due to its pharmacological profile, buprenorphine is not able to exert the same level of agonism (i.e. less reinforcement) as that of methadone and LAAM; this is a result of it possessing antagonist properties. Buprenorphine is therefore not able to equate to the higher dosage levels of methadone, thus substantially reducing the number of patients who are suitable for or willing to be treated with it. Market share penetration projected on the attached spreadsheet is probably generous based on the pharmacological profile of buprenorphine.
4. The pricing of buprenorphine for this indication has obviously not been established, but the attached spreadsheet assumes a patient cost per year of (b) (4). This compares with \$540 for LAAM and \$300 for methadone. Buprenorphine is an expensive compound to manufacture, and the need for a special unit dose sublingual presentation for this indication adds substantially to final product production costs compared to the other two compounds which can be supplied to treatment programs in bulk form (lqt. jars). Typically, the price of such a product would be several times the yearly cost currently projected. However, since the product will be competing in the same marketplace with methadone/LAAM, it would be unlikely to achieve any market share at normal margin price. If we were to increase the projected price, we would have to proportionately reduce the anticipated market penetration. The attached projections are our best efforts to balance these variables.

Based on the above, the spreadsheet is calculated as follows;

1. Sales to Customers = Total Patients (x) (b) (4) 'day.
2. Contribution Before Marketing of (b) (4) for each year based on existing production costs and reviewed by (b) (4).
3. Development Costs are derived from the approved NIH/NIDA CRADA.

4. Fixed and Marketing Costs are internal figures reviewed by (b) (4) See note 3 of (b) (4) certification for details.
5. Cost of Funds represents interest at 10% on the cumulative funds as shown by the projection at year end.
6. Cumulative Return represents our projected return on this investment.
7. BHD Sales = Total BHD patients (x) (b) (4) (x) .365
8. Total Patients derived from FDA/NIDA Notice in Federal Register 20 July

The attached spreadsheet is accompanied by a report from (b) (4) as well as notes provided by them. Also enclosed are copies of relevant pages from the approved CRADA between Reckitt & Colman and NIH/NIDA.

The Orphan Drug Regulations would allow us to calculate all development costs and allocate them based on the indication and geographic distribution of the product. As you can see from the CRADA pages attached, preclinical and clinical studies alone for the development of buprenorphine are valued at about (b) (4). This figure does not include any Reckitt & Colman personnel and overhead costs. Neither does it include the wide range of items which could be considered under the regulations. We've chosen not to include them in the attached spreadsheet because of the difficulty of adequately itemizing and allocating costs which were expended over the past 10 or more years. Needless to say, if included, those costs would further substantiate the fact that we will not derive a profit from this product during the market exclusivity term provided by Orphan Drug designation.

I trust that the attached additional information is sufficient to allow the designation of buprenorphine and buprenorphine/naloxone as orphan products for the treatment of addiction.

If you have any questions, please be in touch with me. You can reach me at the numbers on the letterhead, or my personal number at (804) 379-0907.

Sincerely,



Charles O'Keeffe

Marlene E. Haffner, M.D., M.P.H., Director
Office of Orphan Products Development
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5600 Fishers Lane (HF-35)
Rockville, MD 2085

CBO/alb
enc

11/10/93

Projected Cumulative Return on BHD-Buprenorphine High Dose USA

\$'000	(b) (4)	Note	<u>1993</u>	<u>1994</u>	<u>1995</u>	<u>1996</u>	<u>1997</u>	<u>1998</u>	<u>1999</u>	<u>2000</u>	<u>2001</u>	<u>2002</u>
Sales to Customers	1		(b) (4)									
Contribution Before Marketing	2											
Fixed Costs & Marketing	3											
Net Contribution												
Tax on Net Contribution	4											
Operating Profit after Tax												
Development Costs	5											
Total												
Cumulative												
Cost of Funds	6											
Cumulative Return												

EXHIBIT 17

Review

From morphine clinics to buprenorphine: regulating opioid agonist treatment of addiction in the United States

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Abstract

The practice of prescribing opioid drugs for opioid dependent patients in the U.S. has been subjected to special government scrutiny for almost 100 years. From 1920 until 1964, doctors who used opioids to treat addicts risked federal and/or state criminal prosecution. Although that period ended when oral methadone maintenance was established as legitimate medical practice, public concern about methadone diversion and accidental overdose fatalities, combined with political pressure from both hostile bureaucracies and groups committed to drug-free treatments, led to the development of unprecedented and detailed Food and Drug Administration (FDA) regulations that specified the manner in which methadone (and later, levo-alpha-acetyl methadol, or levomethadyl acetate, (LAAM)) could be provided. In 1974, Congress gave the Drug Enforcement Administration (DEA) additional oversight of methadone treatment programs. Efforts to liberalize the FDA regulations over the past 30 years have been resisted by both the DEA and existing treatment providers. Additional flexibility for clinicians may evolve from the most recent effort to create an accreditation system to replace some of the FDA regulations. The development of buprenorphine, a partial opioid agonist, as an effective treatment for opioid addiction reopened the possibility for having a less burdensome oversight process, especially because of its reduced toxicity if ingested by non-tolerant individuals. New legislation, the Drug Addiction Treatment Act (DATA) of 2000, created an opportunity for clinicians with special training to be exempted from both federal methadone regulations and the requirement to obtain a special DEA license when using buprenorphine to treat addicts. Some details of how the DATA was developed, moved through Congress, and signed into law are described.

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Keywords: Buprenorphine; Methadone maintenance; Office-based pharmacotherapy; Opioid agonists; Regulations; Treatment; History; Policy

1. Early history of opioid-addiction treatment

The federal regulation of medical prescribing of opioids in the U.S. began with the Harrison Act of 1914. While the Harrison Act did not actually prohibit physicians from prescribing opioids for addicted patients within a legitimate medical context, the Treasury officials who were empowered to implement the Act vigorously opposed the practice and were successful in deterring physicians from engaging in it. By 1920, the American Medical Association (AMA) also condemned

prescribing opioids to addicts, thereby opening the door further to the prosecution and conviction of physicians who continued to do so. This difficult situation for people who were dependent on opioids and for the practitioners who wanted to help them did not begin to change until 1964. It was then that Vincent Dole and Marie Nyswander first described their work treating heroin addicts with orally administered methadone (Musto, 1987; Jonnes, 1996).

Some of the milestones of those 50 years between the Harrison Narcotic Act of 1914 and the studies of methadone maintenance in 1964 include the rise and fall of morphine clinics (the last of them closed in 1923); the successful federal prosecution of physicians who prescribed morphine to addicts; and, following a period of relative stability in the 1930s and 1940s, a post-World

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War II rise in heroin addiction that led to new federal legislation increasing the severity of penalties for the use and possession of illicit drugs. In 1961, a report issued by a joint committee of the American Bar Association and the AMA questioned those repressive drug policies and encouraged research on opioid maintenance (Musto, 1987).

Throughout most of this period, and until he retired in 1962, Harry J. Anslinger headed the Bureau of Narcotics. Anslinger believed strongly that addiction would disappear in the face of severe penalties for the possession, use, or sale of drugs, and that getting rid of drugs, drug users, and drug pushers would solve the drug problem. Under Anslinger's influence, demonizing the drugs, especially heroin, became a key element of federal drug policy, and addiction to opioid drugs was portrayed as an incurable disorder that condemned its victims to a life of degradation (Musto, 1987; Courtwright, 1992).

2. Evolution of methadone treatment

The current system of opioid treatment regulations, as well as American attitudes towards addicts, were influenced not only by this history, but also by other equally important elements and events. These included a heroin epidemic that accelerated in the early 1960s; the rise of the therapeutic community movement, which convincingly demonstrated that heroin addicts were not beyond redemption; the Narcotic Addict Rehabilitation Act (NARA) of 1966, which established a federal civil commitment program modeled partly on similar programs in California and New York; and the work of Dole, Nyswander, and their collaborators at the Rockefeller Institute. Their work, from the early 1960s and onward, showed that heroin addicts who were maintained on oral methadone could give up heroin and lead productive, law-abiding lives (Glasscote et al., 1972; Gerstein and Harwood, 1990).

The data reported by Dole, Nyswander, and coworkers, and soon confirmed by others, showed that treatment in methadone treatment programs sharply reduced heroin use and criminal activity, increased gainful work, and resulted in generally improved health. Equally important, patients found the treatment acceptable, and several treatment centers began operation. Most of the treatment centers using methadone operated under Investigational New Drug (IND) applications issued by the Food and Drug Administration (FDA), and thereby claimed exemption from the policies of the Bureau of Narcotics, which still viewed providing opioids to addicts as illegal. It is of historical interest that Dole and coworkers at Rockefeller did not seek or obtain an IND, since they took the position that methadone was an approved therapeutic agent and

that off-label use did not require an IND. From 1967 to 1970, the FDA liberally issued INDs for methadone research. Beginning in 1968, INDs were also issued for the study of LAAM, (levo-alpha-acetyl methadol, or levomethadyl acetate). By 1969, several thousand patients were enrolled in methadone maintenance treatment research programs (Jaffe, 1975; Gerstein and Harwood, 1990; Jonnes, 1996; Kreek and Vocci, 2002).

Yet, methadone was not well received in the early 1970s. Most federal agencies were hostile towards it or were at least skeptical about it. The Departments of Justice and the Treasury, still influenced by Anslinger's vision, saw methadone treatment as wrongheaded. Advocates for psychosocial programs within the treatment community derided it as a 'magic bullet' that was likely to lessen concerns about unemployment, housing, and the psychological and sociological origins of addiction; vocal groups of recovering heroin addicts saw it as both an irrational treatment and a threat to the therapeutic community movement; some minority activists described it as a government effort to control the behavior of young black men.

Even the FDA did not find the data that were generated sufficient to approve methadone as a safe and effective treatment for heroin addiction. Further, there was no rationale for determining how many INDs to issue and no practical mechanism to prevent their misuse as a cover for profit oriented prescribing of methadone unaccompanied by rehabilitative services. No standards had been established for what constituted minimally acceptable treatment, and no rules governed the amount of opioids that could be prescribed, or taken home, or for whom the treatment was appropriate, giving the recipients of the methadone INDs large leeway in making those decisions. Newspapers published stories about physicians who prescribed methadone for patients who were not seriously dependent on opioids; about methadone being diverted from the clinics to the street; and about children being poisoned by drinking methadone that was brought home legitimately by household members who were in treatment. Methadone maintenance also drew criticism from advocates and providers of 'drug-free' treatment, who saw it as another form of addiction, from law enforcement groups, and from minority groups who denounced it as 'genocide' (Jaffe, 1975; Jonnes, 1996).

In June of 1970, the FDA proposed a new ruling on methadone IND applications. Largely a response to the numerous Congressional and community concerns about the issues of diversion of methadone, iatrogenic methadone addiction, and accidental overdoses, the new IND regulations imposed such strict requirements on entry into treatment, dosage, and duration of treatment that they discouraged methadone use. With this ruling, which became final in April, 1971, the FDA avoided making a decision on whether methadone treatment was

safe and effective, but allowed it to continue 'thinly disguised as research.' These stringent regulations were of no help to the many heroin addicts who were seeking treatment but could only be put on waiting lists. The status of methadone treatment as 'research' made government authorities at all levels reluctant to provide funds to support its expansion.

Nevertheless, in June of 1971, the Nixon administration's initiative on drug abuse included the decision to accept methadone maintenance as an effective treatment, to develop ways of minimizing the real and perceived problems with its use, and to expand access to treatment for those who wanted it. The White House Special Action Office for Drug Abuse Prevention (SAODAP) worked with the FDA to revise the overly stringent regulations in order to achieve those objectives. First proposed in April 1972, the new regulations established the basic framework that governed the use of methadone and similar opioid agonist drugs in the treatment of heroin addiction for the following 30 years. These regulations created a hybrid IND–NDA (New Drug Application) that acknowledged the safety and efficacy of methadone maintenance as a treatment, but imposed a number of conditions on how it could be used. Those conditions represented a substantial and unprecedented departure from the usual practice of allowing licensed physicians to use their own professional judgment, guided by a drug's labeling, to determine how to prescribe a medication. Among other things, the 1972 regulations specified, according to various criteria including age and duration of drug dependence, who could be eligible for methadone treatment. They also specified the maximum initial dosages that could be used, the minimum amount of counseling that must be provided, and the factors to be considered when deciding on take home medication, such as how long a patient had been in treatment and whether drug tests showed any evidence of illicit drug use. The new regulations also created a closed system for methadone, restricting its availability to approved clinics and hospital pharmacies, with the aim of deterring those few individual physicians who, in violation of the 1971 regulations, continued prescribing methadone for substantial fees (Jaffe, 1975; Rettig and Yarmolinsky, 1995; Jaffe, 1997; Kreek and Vocci, 2002).

Each element in the 1972 regulations was intended to reduce or prevent problems that had been experienced under the largely informal pre-1971 IND system; or to correct the overly restrictive aspects of the 1971 regulations; or to assure concerned parties, including Congress, that methadone would be used in combination with, not as a substitute for, rehabilitation. In short, the 1972 regulations were designed to allow expansion of treatment while maintaining some control over quality of treatment. They described 'medication units' because they anticipated a time when clinics and individual

practitioners would be linked to pharmacies and other sites that would be authorized to dispense drugs, such as methadone, for the treatment of addiction. The drafters of the regulations did not intend for medication dispensing to be forever limited to a few large clinics. Although they recognized that access to treatment by individual physicians might temporarily be limited, they believed that the regulations would be revised as knowledge expanded and as opioid maintenance treatment became less controversial (Jaffe, 1975, 1997). The regulations became fully effective in March, 1973. However, throughout 1972 and the beginning of 1973, some members of Congress and certain journalists continued to see methadone diversion as a serious problem. In June 1973, the Senate passed the Methadone Diversion Control Act of 1973, which became the Narcotic Addict Treatment Act of 1974 (NATA). This law, which was an amendment of the Controlled Substances Act (CSA), gave the newly created Drug Enforcement Agency (DEA) jurisdiction over the storage and security of drugs used in the treatment of addiction. It also required separate DEA registration annually of practitioners and treatment sites. The Secretary of Health, Education, and Welfare (now Health and Human Services [HHS]) retained the responsibility for setting standards for proper professional practice in the medical treatment of addiction.

Since 1970, clinicians have criticized the Federal regulations as a burdensome interference with the practice of medicine. Some claim that the paperwork burdens and constraints on take-home doses contribute to patients' dropping out of treatment (Dole, 1992). Although some of the criticism is valid, it often fails to distinguish between federal, state, and local regulatory burdens. State and local jurisdictions have also seen fit to enact legislation governing these programs, and some of those regulatory requirements are far more restrictive than federal ones. For example, some localities do not permit any take-home medication. Another criticism is that regulatory oversight is concerned exclusively with process, although actual treatment outcome can be measured. But regulations alone are not responsible for all of the problems methadone treatment providers encounter. Not to be overlooked is the impact of the more than 50% reduction (inflation-adjusted) in the level of financial support for methadone treatment programs in most parts of the country over the past 30 years (Gerstein and Harwood, 1990).

Alternatives to the current regulatory framework have been sought and proposed over the years. There is no federal legislation that requires the Secretary of HHS to issue *regulations* dealing with the medical treatment of 'narcotic addiction.' *Guidelines* could accomplish this task equally well. In 1984, Congress amended the NATA, and gave the DEA authority to withdraw registration from treatment programs or

individual practitioners for committing (in DEA's judgment) 'such acts as would render registration inconsistent with public interest.' Since one federal agency (DEA) already has the authority to revoke licensure, there may be no good reason to have any HHS regulations. However, if the use of opioid agonists in the treatment of opioid dependence were governed only by HHS guidelines or professional judgment, any oversight of the quality of treatment would be left to the discretion of the DEA and to the tort system (Molinari et al., 1994).

In summary, for most of the past 30 years the regulatory framework dealing with the use of opioids in the treatment of addiction in the U.S. has consisted of a dual oversight at the federal level (HHS and DEA), as well as various (and varying) regulatory requirements at the state and local levels. Although the FDA regulations were intended to be more flexible and responsive than legislation to changing conditions, prior to the major revision that was finalized in 2001 they had been revised only twice, in 1980 and 1989. Those changes were relatively minor, mostly having to do with urine testing, on-site services, and easing constraints on admissions. Despite complaints about over-regulation, when the FDA and the National Institute on Drug Abuse (NIDA) issued a proposal in 1983 to convert most regulations to 'guidelines', most of the treatment providers who responded to the proposal stated a preference for the existing regulatory system (Rettig and Yarmolinsky, 1995). In 1989, largely as a response to the spread of HIV among intravenous drug users, NIDA and the FDA published a rule regarding 'interim methadone maintenance'—the provision of methadone without rehabilitative services to addicts waiting to get into full service programs (Rettig and Yarmolinsky, 1995). The methadone treatment providers and some state authorities reacted unfavorably. Many treatment providers believed that interim maintenance would inevitably lead local, state, and federal governments to further reduce funding and to pay only for dispensing methadone (Rettig and Yarmolinsky, 1995).

3. Opioid-agonist treatment regulations—recent changes

The number of patients in methadone treatment programs has grown since the early 1970s, from about 20,000 to about 180,000 (Kreek and Vocci, 2002). Some states still do not permit methadone or other opioid agonist treatment regulated by the NATA. In 1993, when the FDA finally approved LAAM for the treatment of heroin addiction, multiple state and local legislative and regulatory barriers still prevented it from being used. Even where it was permitted its utility was compromised because the FDA regulations that

prohibited take-home doses entirely. (New regulations that took effect in 2001 now permit take-home doses.)

In 1992, the Institute of Medicine (IOM) undertook a review of the Federal regulation of methadone and LAAM in the treatment of addiction. Their report, issued in 1995, concluded (among other things) that the current regulation by multiple agencies: (1) overemphasizes the dangers of methadone diversion; (2) burdens programs with unnecessary paperwork; (3) constrains clinical judgment; (4) reduces access to treatment; and (5) contributes to premature discontinuation of treatment. The IOM recommended that the current detailed regulations be replaced by practice guidelines and sharply reduced regulations (Rettig and Yarmolinsky, 1995).

In response to the IOM recommendations, the federal agencies that comprise the Interagency Narcotic Treatment Policy Review Board (FDA, NIDA, Substance Abuse and Mental Health Services Administration [SAMHSA], Department of Veterans Affairs [VA], DEA, and the Office of National Drug Control Policy [ONDCP]) undertook the work of substantially revising the HHS regulations. The DEA did not propose any changes in its authority to require special licensing and to oversee addiction treatment that uses opioid drugs. Originally, the new system was to have as its central feature a set of HHS regulations requiring programs or practitioners that use opioid agonists for addiction treatment to be accredited by an approved accrediting body, and establishing an upper limit on the amount of opioid medication that could be given to patients for use outside the clinic at any one time. Accrediting bodies would base their decisions on a set of treatment standards approved by the Secretary of HHS, and representing the best clinical thinking of experts in the field, subject to change as knowledge changes. It was recognized at the outset that value judgments and trade-offs are implicit in how standards of care are set. Setting high standards that require competent initial assessments, good medical care, and some minimal level of psychosocial support will limit access for some addicts where states, localities, or insurance carriers are unwilling to pay for those services. If the standards are not met, neither programs nor individual practitioners can be accredited, and the power to accredit becomes the power to destroy. Conversely, if standards are set quite low, the cost of delivering care will be reduced and access may increase; but then it becomes likely that some programs would be no more than opioid dispensaries staffed by the lowest cost personnel, and with considerable risk of hazardous prescribing practices and drug diversion. Unless federal and state priorities were to be reordered so as to provide much greater financial support for opioid treatment, setting standards, whether by guideline or regulation, will involve difficult value judgments.

Some changes have now been approved, but the effort to shift from federal regulations with their implied criminal penalties for violations to a system of peer review accreditation did not result in as much freedom for clinical judgment as those within HHS, who originally proposed the accreditation process, had hoped for. Pressures from already licensed methadone providers and the DEA left in place many of the regulatory constraints on clinical judgment, particularly with respect to the compliance burden placed on virtually all new patients regarding take-home medication and clinic attendance. While the new regulations eased considerably the maximum take-home dosages permitted for long term patients (in treatment for more than 2 years), new patients, regardless of level of stability or need for other treatment services, are still required to obtain nearly all their medication at the clinic for a period of several months. Furthermore, the burdens of meeting the accreditation requirements are likely to prevent individual physicians, no matter how well trained, from using opioid medications such as methadone or LAAM to treat opioid dependent patients in their offices, unless the physician is administratively linked to an existing opioid treatment program. In addition, the NATA still requires all physicians who might wish to treat opioid addicts with Schedule II opioid medications to obtain a separate registration for this purpose from the DEA, even if they intend to treat only a few patients.

Although these latest changes in the regulations, including the institution of accreditation, are far greater than those accomplished by the two previous revisions, their modesty and the time it took to bring them from initial proposal to reality gives testimony to the inertia in the system, the complexity of forces that influence it, and the power of the current stakeholders. The notion of a system of accreditation to replace the regulations was raised by Curtis Wright and Jerome Jaffe at a meeting of the Interagency Narcotic Treatment Policy Committee in 1995, shortly after the release of the IOM report on methadone regulation. It did not get final approval within HHS until some time in December of 2000. There were considerable reservations voiced at ONDCP. Following the Presidential elections of 2000 and the change in administration, a hold was placed on all regulatory change. The modifications of the methadone regulations did not go into effect until May 18, 2001 (N. Reuter, personal communication).

4. Buprenorphine: a new pharmacotherapy for opioid addiction

A major justification for the regulation, accreditation, and separate DEA registration was to minimize the diversion of opioid drugs from treatment programs.

Among the most important concerns about diversion are the serious toxic consequences that ensue when non-tolerant individuals ingest dosages of methadone or LAAM typically used in treatment. As early as [Jasinski et al. \(1978\)](#) had noted the possible clinical utility of buprenorphine, a partial opioid agonist. By the early 1990s, it became clear that buprenorphine could be used effectively for the treatment of heroin addiction ([Johnson et al., 1992](#); [Ling et al., 1996](#)) and that its partial agonist properties resulted in very substantially decreased toxicity even for non-tolerant individuals ([Walsh et al., 1994, 1995](#)). Under these circumstances, one major justification for maintaining the 'closed system' for medications used in opioid maintenance was largely eliminated. It was not so much that diversion of a partial agonist could be considered a trivial issue, but rather that with lethality from diversion of prescribed medication sharply reduced, a fresh look could be taken at the costs and benefits of making opioid treatment both more accessible and less stigmatizing by moving it from the clinics into the offices of individual physicians. It seemed possible that, under the right circumstances and once approved by the FDA for use in the treatment of opioid dependence, buprenorphine might be exempted from some of the burdens associated with the use of methadone and LAAM.

To achieve such an outcome, two major hurdles had to be overcome. First, buprenorphine would have to win FDA approval for the treatment of opioid addiction; second, some regulatory or legislative action was needed that would exempt it from the provisions of the CSA of 1970 and the NATA of 1974. It is important to point out here that from the perspective of Reckitt and Colman (now Reckitt Benckiser Pharmaceuticals), the company that originally developed buprenorphine as an analgesic and still controlled its use, the legislative effort to be described and the effort to develop and win FDA approval for its use in addiction treatment were seen as being inextricably intertwined. It was obvious from the experience with LAAM that winning FDA approval for a drug used in the treatment of addiction in no way assures its utilization if it also requires legislative changes in each of the 50 states. Also, from a corporate perspective it seemed unlikely that a drug confined to a limited number of clinics that were already comfortable using generic methadone would be used enough to justify the investment involved in taking buprenorphine through the regulatory process.

Reckitt and Colman knew it would be at least a 5-year project and that it would be committing millions of dollars to develop a product that had no patent protection remaining. The Board of Directors decided to approve the process nevertheless. It was apparent that, to recover any significant portion of corporate expenditures, two conditions would be needed. First, buprenorphine would need to reach the mainstream

practice of medicine—a goal that certainly seemed achievable in light of the IOM report on methadone regulation. Second, a period of market exclusivity would be needed to protect the product once FDA approved it. The Company faced three challenges. To address the matter of market exclusivity they needed to seek Orphan Drug designation. This was accomplished fairly quickly in 1994. The next challenge was to somehow amend the CSA of 1970 to allow physicians to treat patients with buprenorphine in the normal course of the practice of medicine. This change would result in an exemption from the NATA, which is itself a modification of the CSA. The third was to submit an NDA to the FDA and gain its approval. What follows here is the story of how the legislation that largely exempts buprenorphine from certain provisions of the CSA made its way through Congress to the Oval Office.

5. A need for new legislation

Reckitt and Colman was convinced by the history of efforts to modify the methadone regulations that amending treatment program regulations through administrative change would be a long and cumbersome process unlikely to reach the goal of moving treatment into the mainstream of medicine and expanding access for new patients. The company therefore chose to seek a change in the law. The original aim of the proposed legislative solution seemed simple and straightforward: to change the law to waive the current requirements for physicians prescribing opioids to treat opioid dependence. The proposed legislation would leave the methadone system intact but expand the possibilities for treatment. The original draft of this legislation, called the Drug Maintenance and Detoxification Act, was written by Charles O'Keeffe and Robert Angarola in October, 1995. That first draft stated simply that the requirements of the CSA did not apply when a physician treated no more than 20 patients with a Schedule V narcotic. As it turned out, this proposed legislation went through many changes and was not finally passed by Congress until 2000. It took more than 5 years to enact a very minor amendment to the existing legislation.

The high points of that journey make an interesting lesson about the process of change in our democracy. In 1995, representatives of Reckitt and Colman approached Capitol Hill offices to explain the issue as they saw it: there is a new product which, when approved, will have the potential to bring a significant number of new patients into treatment. But there will be no market for it and the medical community will not be able to use it because of current legal requirements. In several offices, staff members were very receptive.

Senator Carl Levin, who has had a long standing personal interest in expanding and improving addiction

treatment, became a supporter. Senator Orrin Hatch and his staff on the Senate Judiciary Committee, which has jurisdiction over the Controlled Substance Act, was also interested. Senator Joseph Biden, who had previously introduced legislation to encourage the development of new addiction treatment medication, was most interested. Strong allies in the House of Representatives included Congressman Thomas Bliley, who was then Chairman of the Commerce Committee, which shares jurisdiction over the CSA with the Judiciary Committee. With their efforts, several key members of the Judiciary Committee and others on both sides of the aisle became persuaded that the proposed legislative changes would be good policy. Despite this promising start, it was not until the end of the 1998 congressional year that the Company could rally enough support to get something going. But 1998 was an election year and the end of the 106th Congress. It was clear that the bill could not be enacted using the full legislative route. Senate staff suggested an alternate approach: using what is called a 'must-do' vehicle: that is, attaching it to a bill not necessarily related to the subject matter, but one such as an appropriation bill that must be signed into law. Senator Hatch's staff, with agreement from the offices of Senators Levin, Biden and Moynihan, arranged to have the proposed change to the CSA tucked into a multiagency appropriations bill for Senate action. This required negotiating with HHS, Justice, and the White House over provisions of the bill. The parties reached agreement in late October 1998, about 3 years after the original draft was written. Although Chairman Bliley of the House Commerce Committee was willing to let this amendment pass as part of the appropriations bill, the senior Democrat member of that committee, Congressman John Dingell, was not. He objected to the process, not the policy. He said the Committee had never held hearings on the matter and had never formally considered the legislation, and this, he said, deprived the members of the Committee of an opportunity to examine the policy, understand it, and either agree or disagree with it. He also noted that appropriations bills are not the place to change health care policy. The provision was removed from the bill.

Shortly thereafter the bill's supporters in the Senate produced a new draft of the legislation. This time the Company and the involved congressional staffers tried to follow everyone's rules. They worked with virtually all of the interested parties, including the Clinton administration, FDA, SAMHSA, NIDA, DEA, and the departments of HHS and Justice. FDA was concerned that the system could get out of hand unless limits were placed on the number of doctors and patients who initially could participate in the system. DEA worried that they would not be able to get a handle on whether physicians were appropriately registered. SAMHSA was concerned about the impact on

their resources and about the potential impact on current methadone clinics. The College on Problems of Drug Dependence (CPDD), the American Methadone Treatment Association (AMTA), the American Academy of Addiction Psychiatry (AAAP), the American Society of Addiction Medicine (ASAM), the American Psychiatric Association (APA), the AMA, the American Osteopathic Association (AOA), and others in the field, also had concerns and suggestions.

The new bill was introduced at the end of January, 1999, by Senators Hatch, Levin, and Biden. It provided that physicians who were qualified to treat opioid-dependent patients would be allowed to prescribe certain FDA approved opioids without being subject to current regulations, so long as they certified to their qualifications with the Secretary of HHS 30 days in advance of treating such patients and treated no more than 20 at a time. The bill also provided that the new federal paradigm would not be pre-empted by the states for at least a period of 3 years, but gave the Secretary of HHS and the Attorney General ample authority to stop the entire program if there was significant abuse. It was passed by the full Senate in November. Still needed was a House bill and agreement between the House and Senate, but some people on the Democrat side of the House were still irritated by the ill-fated effort to put the matter into an appropriations bill the year before. Congressman Dingell had written to the Secretary of HHS, Donna Shalala, raising questions and concerns about the buprenorphine bill that needed to be addressed before there could be further movement. Fortunately, Secretary Shalala responded in support of the policy change. She argued for changing the regulatory framework of drug treatment, for destigmatizing treatment, and for the promise of new treatment products such as buprenorphine. This was a positive development, but it was not until the end of July of 1999 that a bill was finally introduced into the House of Representatives. A hearing was held on July 30th, and although one witness raised concerns about the impact of new treatment arrangements on the current methadone system, and another raised the issue of whether insurance would cover new treatments, the witnesses were otherwise quite positive. Significantly, Senators Hatch and Levin testified in the House of Representatives in support of the bill. Dr Westley Clark, of the Center for Substance Abuse Treatment (CSAT), testifying for SAMHSA, noted the importance of ensuring that states would follow any new federal oversight arrangement from the outset to make certain it caught hold. He cited the LAAM experience as an example of how not to get new interventions broadly adopted. Another 3 months passed before the Commerce Committee acted and the bill was ready for House consideration. During that time various changes were made to the bill, including, for example, greater specificity about what makes a provi-

der 'qualified'. Although state preemption remained a concern for some members, the final language was believed to provide sufficient opportunity after an initial transition period for states to make different rules.

Meanwhile, a bill aimed at shutting down illicit methamphetamine laboratories had been introduced into the Senate by Senator John Ashcroft and was arousing interest and support. This interest was shared by many House members as well, and it now gained priority in both the House and Senate Judiciary Committees. Thus, before the Drug Addiction Treatment Act (DATA) of 2000, or the 'Buprenorphine bill', as it came to be known, could be released, some activities on methamphetamine, including hearings in members' home districts, had to be undertaken. Furthermore, the members wanted to ensure that the methamphetamine bill would sail through the legislative process. This required a considerable amount of negotiation about both bills among interested parties. The House finally considered the buprenorphine bill on July 18, 2000 under 'Suspension of the Rules'. Under this procedure, only 1 h of debate is allowed and no amendments are accepted. While it is more predictable than a process where multiple amendments can be offered, under this procedure a two-thirds vote, rather than a simple majority, is needed to pass a bill, and for this reason the committee was concerned that the bill not be controversial. The debate was held, the bill was supported, and it seemed poised to be passed by the House on a voice vote, when Chairman Bliley made a motion to require a roll call vote to take place later that day. Then another glitch appeared: the version of the bill printed in the Congressional record was different from the version that had been considered on the House floor. This administrative error meant the bill would have to lay over until the next day at least.

Although the Secretary of HHS had been supportive, the DEA had serious reservations, and the 1-day layover gave them another opportunity to voice their concerns. They immediately contacted the House Judiciary Committee and attempted to add a requirement for physicians to register separately with the DEA or to get DEA approval before prescribing. The effort failed. The bill passed the House the next day with a vote of 412 to 1. It was then placed on the Senate calendar, but before it could come to consideration, the Senate Judiciary Committee passed the methamphetamine bill and attached to it their version of the buprenorphine bill. The Senate now had its own bill, quite different from the House version, a methamphetamine/buprenorphine bill, which it passed and sent to the House on January 27, 2000. Although the buprenorphine amendment to the CSA had now been passed by both House and Senate, there was still no law on the books that actually changed policy.

Throughout this process, staffers in the offices of Senators Hatch, Levin and Biden were seeking other vehicles for both the methamphetamine and buprenorphine bills. Ultimately, both bills were included in another 'must pass'—a huge bankruptcy reform bill. The House and Senate were in conference on this bill. Bankruptcy reform was hardly benign and the conference was not without some rancor. Senator Levin was determined to pass the buprenorphine bill, with or without the methamphetamine bill. As the ranking member of the Senate Armed Services Committee, and with the concurrence of the chairman of that committee, Senator John Warner, he had the buprenorphine bill placed in the Department of Defense Authorization conference, attached to another 'must pass' bill to allow the military to continue to function.

In the spring of 2000, there were six versions of the buprenorphine bill making their way through the legislative process: two versions of a stand-alone buprenorphine bill; two versions of a buprenorphine/methamphetamine bill; a buprenorphine/bankruptcy bill; and a buprenorphine/guns bill. Then events took another amazing turn. On May 9, 2000, the House passed a bill, H.R. 4365, to 'amend the Public Health Service Act with respect to children's health'. Without fuss or fanfare, this combination of several children's health bills was scheduled for action. It was now Chairman Bliley's chance to seize an opportunity; so H.R. 2634, Bliley's buprenorphine bill, became part of what came to be known as the 'Children's Health Act'. The House passed their bill and sent it to the Senate. After some behind the scenes negotiations, the bill passed the Senate on September 22, 2000, with an amendment that was, not surprisingly, the Senate version of the buprenorphine bill with the methamphetamine provisions. That amended bill, of course, had to be sent back over to the House and reconsidered. The House passed the bill exactly as the Senate had passed it, as Public Law 106–310, on September 27, 2000. On October 17th, President Clinton signed it into law. It is of some academic interest that the bankruptcy bill and the defense authorization conference were still in play, so at the last minute the buprenorphine provisions had to be snatched out of those bills. The President vetoed the bankruptcy bill on December 19, 2000.

6. The drug addiction treatment act of 2000

The new law, the DATA of 2000, offers an opportunity to make significant changes in the way addiction treatment is delivered. The change could be of benefit to hundreds of thousands of patients addicted to opioids. Perhaps as result of this legislation, other companies will see more opportunity in the development of new pharmaceuticals to treat addiction. The last hurdle was

the final approval of the buprenorphine NDA by the FDA.

Buprenorphine for the treatment of opioid dependence was approved on October 8, 2002. This approval marks a new milestone in the evolution of the American response to opioid addiction, but it does not mark our crossing into therapeutic utopia. There will be problems. With FDA's approval of buprenorphine we will have, concurrently, two distinct oversight systems that deal with the use of opioid drugs in the treatment of opioid addicts. One is the modified set of regulations that emerged from the hybrid IND–NDA that developed and evolved over 30 years to provide a framework for oversight of methadone treatment. That system, which applies to all Schedule II opioids, such as methadone and LAAM, now incorporates a system of professional accreditation to oversee some aspects of treatment quality. It would not be inaccurate to describe this system as a hybrid–hybrid. And it still includes, by federal regulation, numerous constraints on the free exercise of judgment by treating clinicians. The other oversight system is the set of conditions that will govern the use of Schedule III–V opioid drugs, such as buprenorphine, that are approved for the treatment of addiction by the FDA. In this system, the judgment of the clinicians, who must attain certain qualifications or special training in order to be exempt from certain requirement of the NATA, is constrained by the requirement to limit the number of patients treated at any one time and the restriction on group practices.

7. Future challenges

It is not clear at this time how these two concurrent systems will interact and what the impact will be on patient access to treatment or the array of services provided. It is anticipated that the changes in the older system (the hybrid–hybrid) and the availability of buprenorphine in the offices of qualified physicians will serve both to increase access to treatment and to ease the compliance burdens on patients, and that both of these conditions will result in substantial benefits to the public and patients treated. But the law of unintended consequences has not been repealed, and it will remain for future commentators to judge what has been brought by these policy changes.

Undoubtedly, there will be some diversion of buprenorphine, and there will be some overdoses. We hope that few, if any, are fatal. Some young people will try buprenorphine and find it reinforcing. Somewhere, someplace, these events will be reported on by the media. It is difficult to predict the spin that such news will be given. The published articles and the television programs will probably not mention that in France the widespread therapeutic use of buprenorphine for the

treatment of 70,000 heroin addicts seems to have reduced significantly the opioids overdose death rate (Ling and Smith, 2002). What the coverage might underscore is that, other than peer pressure, neither government nor the medical profession will have mechanisms to deal with the individual rogue physician who prescribes inappropriately or too generously. If such behavior persists there is, at the federal level, only the extreme measure of reconsidering the status of buprenorphine as a Schedule III drug, or of the provisions of the Drug Abuse Treatment Act of 2000. What happens, of course, will reflect the peculiar American ambivalence about the opioid addict as not quite a patient and not quite a criminal. Thus, Americans seem willing to tolerate occasional untoward events and misuse of drugs for treatment of hyperactivity or anxiety, but not those associated with treatment of opioid addiction. The most optimistic scenario is that the use of buprenorphine in office based settings will simply increase access and lead the United States to a more pragmatic attitude towards dealing with the consequences of heroin addiction—and that such pragmatism will be long lasting and will demonstrate what can be achieved by easier and less stigmatizing access to treatment. With continued support from NIDA and CSAT, the new era of clinical freedom will be just another step in the long national effort to achieve the right balance between investing in supply control and demand reduction.

Acknowledgements

Charles O'Keeffe is President of Reckitt Benckiser Pharmaceuticals. Jerome Jaffe retired from his position as Director of OESAS in CSAT in 1997. He was a consultant to Schering Corporation, in 2000–2001, which is licensed by Reckitt Benckiser to market buprenorphine in several countries around the world. In the early 1990s, he provided consultation to drug manufacturers Roxane and Mallinckrodt, which manufacture and distribute methadone and LAAM. Support for this work was provided through internal funds only.

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EXHIBIT 18

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NOV 18 2000

RECKITT & COLMAN
PHARMACEUTICALS
INC.

November 6, 2000

Office of Orphan
Products Development

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Orphan Product Applications:
[REDACTED]

Dear Sir or Madam:

This is an annual report on the status of our development of a combination of buprenorphine and naloxone for the treatment of drug addiction (Orphan product application [REDACTED])

Clinical studies of this pharmaceutical product have been completed, and New Drug Application 20-733 was submitted to the FDA on June 7, 1999. It was filed 60 days later and is now under active review. This application has a review priority classification of P (priority.) An "approvable" letter dated 12/07/00 was received from the FDA and an amendment/response was submitted 07/28/00. Approval of the application is expected before the end of 2000 or early in 2001.

NDA 20-732 for the mono product (Orphan product application [REDACTED]) is now under active review by the Food and Drug Administration. The new drug application was submitted on March 31, 1997. A letter from the FDA dated June 30, 1998 notified us that the NDA is approvable pending submission of the report on the multi-center study and additional information. All information specified by the reviewing division has been submitted. A second "approvable" letter was received on 01/28/00. An amendment/response was submitted on 07/28/00. Approval of the application is expected before the end of 2000 or early in 2001.

We are not aware of any change in the development or marketing plans that will affect the orphan status of either designated orphan product.

Sincerely,

Alan N. Young

Alan N. Young
Director, Regulatory Affairs

January 4, 2002

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

FILE COPY

JAN 11 2002

Ref: Orphan Product Applications:
[REDACTED]

Dear Sir or Madam:

This is an annual report on the status of our development of a combination of buprenorphine and naloxone for the treatment of drug addiction (Orphan product application #93-790).

Clinical studies of this pharmaceutical product have been completed, and New Drug Application 20-733 was submitted to the FDA on June 7, 1999. It was filed 60 days later and is now under active review. This application has a review priority classification of P (priority.) An "approvable" letter dated 12/07/00 was received from the FDA and an amendment/response was submitted 07/28/00. A second "approvable" letter was received dated 01/26/01. A response to this letter has been submitted. Approval of the application is expected in early 2002.

NDA 20-732 for the mono product (Orphan product application #93-752) is now under active review by the Food and Drug Administration. The new drug application was submitted on March 31, 1997. A letter from the FDA dated June 30, 1998 notified us that the NDA is approvable pending submission of the report on the multi-center study and additional information. All information specified by the reviewing division has been submitted. A second "approvable" letter was received on 01/28/00. Several amendments/responses have been submitted. Approval of the application is expected in early 2002.

It was hoped that both applications would be approved in 2001, but the reviewing division has continued to raise questions about various aspects of the manufacturing and distribution of these products.

We are not aware of any change in the development or marketing plans that will affect the orphan status of either designated orphan product.

Sincerely,

Alan N. Young
Alan N. Young
Director Regulatory Affairs

October 14, 2002

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Ref: Orphan Product Applications:
[REDACTED]

Dear Sir or Madam:

It gives me great pleasure to submit this report on Subutex (orphan product application [REDACTED]) and Suboxone (orphan product application [REDACTED]) for the treatment of drug addiction.

As I reported in my update last January, both NDAs were under active review and were approaching approval. The approval came in a letter dated October 8, 2002. An introduction date has not been set, but both products should be available for use in the near future.

We are not aware of any change in the development or marketing plans that will affect the orphan status of either designated orphan product.

Sincerely,

Alan N. Young
Alan N. Young
Director Regulatory Affairs