IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC.,

Plaintiff,

v.

AVADEL CNS PHARMACEUTICALS, LLC,

Defendant.

PUBLIC VERSION:
FILED SEPTEMBER 13, 2022

C.A. No. 21-691-GBW

[redacted]

DEFENDANT AVADEL CNS PHARMACEUTICALS, LLC'S MOTION TO EXPEDITE CONSIDERATION OF ITS RENEWED MOTION FOR PARTIAL JUDGMENT ON THE PLEADINGS

I. INTRODUCTION

Cognizant both of this Court's heavy case load and the recent re-assignment of this case to a new District Judge, Avadel is nonetheless compelled to respectfully request expedited consideration of Avadel's pending Renewed Motion for Partial Judgment on the Pleadings pursuant to Fed. R. Civ. P. 12(c) (D.I. 117) ("Avadel's 12(c) Motion") seeking delisting of Jazz's U.S. Patent No. 8,731,963 (the "'963 patent") from the FDA Orange Book. Jazz informed Avadel that it opposes. As explained further below, Jazz is using the improperly-listed '963 patent to block Avadel from obtaining final FDA approval of LUMRYZ®, Avadel's novel oxybate drug formulation for the treatment of narcolepsy. The fact that Jazz resists the prompt resolution of Avadel's fully briefed 12(c) Motion says it all. Jazz knows that justice delayed is justice denied for Avadel. Put simply, Avadel is unduly harmed each day that the '963 patent remains improperly listed and the FDA is blocked from approving Avadel's novel narcolepsy treatment. As a result of the delay in getting its only revenue-generating product to market, Avadel has already had to cut nearly half of its workforce, [redacted]. Ex. A.

This Court has expedited the resolution of motions in similar circumstances such as this, where accelerated decision-making can ameliorate undue harm to one party without unfairly prejudicing the other. *See, e.g.*, Ex. B (*Westinghouse Air Brake Tech. Corp. v. Siemens Industry, Inc.*, C.A. No. 17-1687-LPS, D.I. 94) (Oral Order granting request to expedite consideration of motion to strike); Ex. C (C.A. No. 17-1687-LPS, D.I. 93) (letter requesting expedited relief); Ex. D (*EIS Inc. v. IntiHealth Ger GmbH*, C.A. No. 19-1227-LPS, D.I. 145) (Oral Order granting request for expedited briefing on motion for temporary restraining order and preliminary injunction); Ex. E (D.I. 141, EIS letter requesting expedited briefing); Ex. F (*AstraZeneca Pharmaceuticals LP v. Becerra*, C.A. No. 21-27-LPS, D.I. 32) at 22 (Judge Stark indicating that

the Court is "leaning towards expediting" briefing on Plaintiff's summary judgment motion challenging HHS advisory opinion); Ex. G (*AstraZeneca*, C.A. No. 21-27-LPS, D.I. 71) (Oral Order expediting hearing on Plaintiff's motion). Indeed, shortly before the reassignment of this case, Judge Noreika ordered expedited briefing on Avadel's 12(c) Motion, requiring Jazz to file a substantive opposition to Avadel's renewed 12(c) motion in two business days. D.I. 151.

For the reasons that follow, Avadel respectfully requests that the Court exercise its inherent discretion to manage its docket and expedite consideration of Avadel's 12(c) Motion consistent with FEDERAL RULE OF CIVIL PROCEDURE 1.

II. BACKGROUND: THE HATCH-WAXMAN ACT, THE PARTIES' RESPECTIVE PRODUCTS, JAZZ'S '963 PATENT, AND AVADEL'S DELISTING MOTION

Avadel is a company dedicated to improving the lives of patients suffering from narcolepsy, a condition characterized by disrupted sleep at night and uncontrollable sleep periods during the day. Avadel has spent years and hundreds of millions of dollars[1] developing a novel drug called LUMRYZ, which allows narcoleptic patients to take a single dose of oxybate at bedtime to help them fall asleep and stay asleep throughout the night. Existing oxybate treatments for narcolepsy, such as Jazz's Xyrem product, require patients to take one dose at bedtime and set an alarm to forcefully awaken partway through the night to take a second dose. As the first once-nightly oxybate product, LUMRYZ stands to eliminate the burden and inherent safety and compliance problems of twice-nightly oxybate products like Xyrem, and address patient demand for a narcolepsy treatment that allows for an uninterrupted night's sleep.

Avadel submitted a New Drug Application ("NDA") for LUMRYZ in 2020 pursuant to § 505(b)(2) of the FD&C Act. While Avadel's product contains the same active ingredient, oxybate,

[1] *See, e.g.*, Ex. H (Avadel 2019 10k excerpt); Ex. I (Avadel 2020 10k excerpt); Ex. J (Avadel 2021 10k excerpt).

as Jazz's—and its approval relies in part on safety studies for oxybate performed by Jazz—Avadel's product uses a novel oxybate formulation that permits once-nightly dosing. It is not a copy-cat or generic version of Jazz's product. Jazz nevertheless is seeking to prevent LUMRYZ from reaching patients, and commenced the first of several patent infringement suits against Avadel in May of 2021, asserting, among others, the '963 patent, the only one of Jazz's asserted patents listed in the FDA's Orange Book.[2] In turn, the FDA required Avadel to submit a "Paragraph IV certification" stating that Jazz's '963 patent is invalid or will not be infringed by LUMRYZ. Ex. K (Correspondence from FDA) at 12; 21 U.S.C. § 355(b)(2)(A)(iv). As a result of this certification (which Avadel maintains was neither necessary nor proper)[3], Jazz could obtain an automatic stay of FDA approval of LUMRYZ until the expiration of the '963 patent in June 2023 simply by suing Avadel for patent infringement within 45 days. Jazz did so but filed suit in a *separate* action for the sole purpose of triggering the statutory stay—not to actually litigate the '963 patent, which has been part of this litigation for over a year.[4] Indeed, nearly nine weeks after suing Avadel, Jazz has not even bothered to serve the complaint in that action. Jazz is gaming the system, and not for the first time.

Avadel's 12(c) Motion is directed to Jazz's attempt to keep Avadel off the market by improperly listing the '963 patent in the Orange Book so that the FDA would require a patent certification from Avadel, and stay approval of LUMRYZ. Only patents that cover a drug or method of using a drug may be listed by drug manufacturers in the Orange Book. 21 U.S.C. §

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[2] The Orange Book provides a list of patents that the holder of a New Drug Application believes covers the active ingredient, formulation, or method of using the drug product covered by the NDA. *Caraco Pharm. Labs. Ltd. v. Novo Nordisk AS*, 566 U.S. 399, 405-06 (2012).

[3] Avadel has filed a suit against the FDA challenging its requirement that Avadel submit that certification, which is pending in the United States District Court for the District of Columbia.

[4] C.A. No. 22-0941.

355(b)(1)(A)(viii). However, companies like Jazz are able to unilaterally misrepresent the claimed subject matter of their patents and wrongfully list them in the Orange Book, and the FDA lacks the authority to second-guess such misrepresentations. *Caraco Pharm. Labs. Ltd. v. Novo Nordisk AS*, 556 U.S. 399, 406-07 (2012). As a result, Congress created a path for parties in Avadel's shoes to obtain relief from the district courts. *Id*. Specifically, parties sued for infringement on improperly listed patents may bring a counterclaim seeking delisting of patents that do not claim a "drug" or "method of using [a] drug" pursuant to 21 U.S.C. § 355(c)(3)(D)(ii)(I).

The '963 patent should be delisted because it does not fall in either of the statutorily enumerated categories. Jazz's '963 patent is directed to a "computer-implemented system for treatment of a narcoleptic patient" and recites various components of said computer system that promote safe distribution of a drug having the potential for misuse.[5] Ex. L ('963 patent) at claim 1. Despite the plain language of the claims—which recite computer-implemented *systems*—Jazz has tried to recast the '963 patent claims as a "*method* of using [a] drug" in attempt to claim its Orange Book listing is proper.

In response, Avadel filed a counterclaim seeking "an order requiring [Jazz] to correct or delete" patent information listed in the Orange Book "on the ground that *the patent does not claim* either—(aa) the drug for which the [brand's NDA] was approved; or (bb) *an approved method of using the drug*." 21 U.S.C. § 355(c)(3)(D)(ii)(I); *Caraco*, 566 U.S. at 408-09 (emphasis added). Avadel's 12(c) Motion seeks to adjudicate that counterclaim, so that FDA may remove the improperly-listed '963 patent from the Orange Book and lift the stay on a final regulatory approval decision for LUMRYZ. D.I. 118 at 11. Avadel's motion concerns the straightforward question of

[5] Jazz asserts that the claims of the '963 patent cover a "Risk Evaluation and Mitigation System" ("REMS"), which is a safety program required by the FDA for certain high-risk drugs to ensure that their benefits outweigh their potential harm.

whether the '963 patent claims "a method of using [a] drug."[6] That question can be answered in one of two ways: (1) by resolving a single claim construction question for '963 patent in Avadel's favor; or (2) by assessing the plain language of Jazz's proposed claim construction. Either way, the '963 patent cannot be shoehorned into covering a method of using a drug, despite Jazz's best attempts.

Avadel initially filed its motion to delist the '963 patent in July of 2021. D.I. 20. Judge Noreika determined that the motion raised a claim construction dispute, and accordingly postponed decision on the motion until claim construction. D.I. 55. Since then, the parties have fully briefed their claim construction disputes, including whether the claims of the '963 patent cover systems or methods. D.I. 132 at 46-66. Avadel also filed its renewed motion for judgment on the pleadings so that its delisting motion could be decided concurrently with claim construction. D.I. 117, 118. Rather than responding substantively to Avadel's 12(c) Motion, Jazz filed a procedurally improper "objection," contending that Avadel was required to seek leave before filing its motion. D.I. 124.

On August 23, 2022, the Court indefinitely postponed the *Markman* hearing, which was originally set for August 31, 2022. D.I. 146. Because resolution of the '963 patent's "systems versus method" claim construction dispute in Avadel's favor would likewise resolve its delisting motion in its favor, Avadel immediately wrote to the Court seeking an expedited hearing on just the REMS patent. D.I. 150. That same day, the Court ordered Jazz to file a response on the merits to Avadel's renewed 12(c) Motion within two days, implicitly acknowledging the urgency of Avadel's request, and rejecting Jazz's procedural objections. D.I. 151. Jazz filed its opposition to Avadel's 12(c) Motion (D.I. 153) within the proscribed two days, and Avadel promptly filed its reply before the next business day (D.I. 154). Jazz subsequently filed a request for leave to file a

[6] There is no dispute that the '963 patent does not claim a "drug."

sur-reply (D.I. 155), and Avadel responded to Jazz's request (D.I. 157). Jazz did not submit a reply in support of its motion for leave, and the time has passed for it to do so. As such, briefing on Avadel's 12(c) Motion is complete, and ripe for resolution. Given the flurry of activity initiated by Judge Noreika after receipt of Avadel's letter, Avadel believed that the 12(c) Motion was being given expedited consideration. In light of the reassignment of this case to a new District Judge, Avadel is compelled to formalize its request for expedited consideration now.[7]

III. AVADEL IS BEING UNDULY HARMED BY JAZZ'S IMPROPER '963 PATENT ORANGE BOOK LISTING AND PATIENTS ARE PAYING THE PRICE

Jazz's opposition to Avadel's request for prompt resolution of an already-briefed motion speaks volumes about its intentions. During the parties' meet and confer, Jazz provided no justification for its opposition to Avadel's request for the simple reason that none exists, other than to further delay a ruling that the '963 patent should be removed from the Orange Book and disrupt Jazz's decades-long monopoly on the oxybate market. Indeed, public stock analyst reports recognize the obvious: delay of approval for LUMRYZ uniquely benefits Jazz. Ex. M.

[redacted] After spending *hundreds of millions of dollars* to develop LUMRYZ, Avadel must continue [redacted] with no incoming revenue from LUMRYZ, its only product. Ex. A. The continued delay in Avadel's market launch has already forced the company to engage in drastic cost-cutting measures, including terminating nearly 50 percent of its work force in June of 2022. *Id.* [redacted]

[7] As yet another delay tactic, Jazz has suggested that it will seek discovery prior to responding to this motion. Discovery is not needed for resolution of a simple request to expedite a fully briefed motion.

[redacted]. If Avadel cannot launch LUMRYZ, [redacted]

See Ex. N at 2.

In addition to the damage to Avadel as a company, delaying the launch of Avadel's product harms narcolepsy patients. As explained above, individuals suffering from narcolepsy are limited to Jazz's oxybate products, which require patients to set alarms and forcefully awaken in the middle of the night to take medication for treatment of their sleep disorder. Ex. O at 1. This treatment plan for patients already suffering from disrupted sleep is counterproductive and wrought with safety concerns, and many patients struggle to comply with this twice-nightly dosing requirement. Ex. P at 1. Indeed, some narcolepsy patients must forgo treatment with oxybate because they cannot comply or consider it unsafe to do so—among other issues, the twice-nightly regimen requires leaving the second dose of this controlled substance with abuse potential sitting on a nightstand for several hours, where children or roommates can access it. Ex. Q (Submission to FDA) at 3. LUMRYZ provides a once-nightly oxybate treatment that avoids the difficulties of Jazz's twice-nightly dosing regime and provides patients with a much-needed improved narcolepsy treatment that allows for a full nights' sleep.

Jazz's improper listing of the '963 patent in the Orange Book and its continued gamesmanship meant to delay approval for LUMRYZ should be brought to an end. Avadel's fully briefed Rule 12(c) motion seeks to do just that and allow Avadel to market its transformative drug product for patients suffering from narcolepsy. Avadel therefore respectfully seeks a just and speedy resolution of Avadel's 12(c) Motion and the parties' dispute regarding the Orange Book listing of the '963 patent.

IV. AVADEL MERELY REQUESTS EXPEDITED CONSIDERATION OF THE RULE 12(C) MOTION

This Court has broad discretion to manage its docket. *In re Fine Paper Antitrust Litigation*, 685 F.2d 810, 817 (3rd Cir. 1982). FEDERAL RULE OF CIVIL PROCEDURE 1 provides that the rules in all civil actions "should be construed, administered, and employed by the court and the parties to secure the just, speedy, and inexpensive determination of every action and proceeding." Avadel's motion asks the Court to exercise its discretion to grant expedited consideration of Avadel's 12(c) Motion to secure its just resolution and minimize ongoing harm to Avadel. As described above, this Court has done so in the past. *See, e.g.*, Ex. B (*Westinghouse Air Brake Tech. Corp. v. Siemens Industry, Inc*., C.A. No. 17-1687-LPS, D.I. 94) (Oral Order granting request to expedite consideration of motion to strike); Ex. C (C.A. No. 17-1687-LPS, D.I. 93) (letter requesting expedited relief); Ex. D (*EIS Inc. v. IntiHealth Ger GmbH*, C.A. No. 19-1227-LPS, D.I. 145) (Oral Order granting request for expedited briefing on motion for temporary restraining order and preliminary injunction); Ex. E (C.A. No. 19-1227-LPS, D.I. 141, EIS letter requesting expedited briefing); Ex. F (*AstraZeneca Pharmaceuticals LP v. Becerra*, C.A. No. 21-27-LPS, D.I. 32) at 22 (Judge Stark indicating that the Court is "leaning towards expediting" briefing on Plaintiff's summary judgment motion challenging HHS advisory opinion); Ex. G (*AstraZeneca*, C.A. No. 21-27-LPS, D.I. 71) (Oral Order expediting hearing on Plaintiff's motion).

Avadel respectfully submits that the atypical circumstances of this motion and ongoing harm warrant expedited relief. That Jazz is resisting Avadel's plea for an expedited resolution of a fully-briefed motion that was previously well on its way to resolution is yet another reflection of Jazz's litigation gamesmanship. While Avadel is confident it will prevail on the merits, [redacted]

V. CONCLUSION

For the reasons stated above, Avadel respectfully requests that the Court expedite resolution of its renewed motion for partial judgment on the pleadings (D.I. 117), and, if needed, hold a brief *Markman* hearing to resolve the above-referenced claim construction dispute by the end of September.

Dated: September 12, 2022

MCCARTER &ENGLISH, LLP

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EXHIBIT A

BIOTECH

With narcolepsy approval a year out, antsy Avadel slashes staff by 50%

By **Max Bayer** • Jun 30, 2022 11:04am

Avadel Pharmaceuticals | Food and Drug Administration (FDA) | narcolepsy | New Drug Application

Avadel's cost-saving measures are meant to extend the company's $100 million cash runway. (Andrei Askirka/Getty Images)

Staring down the barrel at a potential year-long wait for full approval for a narcolepsy drug, Avadel is getting antsy with regulators and slashing staff to buoy its cash runway ahead of a commercial launch.

The company has elected to cut nearly 50% of its staff to save as much as $14 million a quarter, according to an announcement Thursday. As the company has ramped up commercial efforts for FT218, operating costs have more than doubled in the first quarter of 2022 topping $21.6 million compared to the same quarter a year ago. The layoffs are expected to extend Avadel's $100 million cash runway, but will also result in a $3-4 million restructuring charge due primarily to severance costs.

The downsizing underscores how Avadel is taking every measure possible to save cash ahead of the commercial launch for FT218, a once-nightly treatment for excessive daytime sleepiness or cataplexy in patients with narcolepsy. It follows a decision by the FDA last month to request certification of Avadel's Risk Evaluation and Mitigation Strategy (REMS) patent. Such patents are used to validate a REMS program, a plan outlined by drug manufacturers to assuage fears of adverse safety events. Requiring additional certification is what delayed the approval timeline for FT218 into 2023.

"Nearly every day we hear from disappointed patients who are waiting for a once at bedtime oxybate treatment option," said CEO Greg Divis in a statement. The company, too, is chomping at the bit, pursuing "every available pathway to accelerate the decision" by the FDA.

EXHIBIT B

ORAL ORDER: Having reviewed Defendant's request for expedited consideration of its Motion to Strike or in the Alternative for Leave to File a Sur-Reply and to Extend Hearing Date (D.I. 92, 93), IT IS HEREBY ORDERED that expedited consideration is GRANTED. Plaintiff shall file a letter, not to exceed three pages, responding to Defendant's motion by tomorrow at 11:00 AM. Today's deadline for the parties' joint letter to the Court regarding issues for the pre-hearing teleconference is CONTINUED. ORDERED by Judge Leonard P. Stark on 6/19/18. (ntl) (Entered: 06/19/2018)

As of June 20, 2018, PACER did not contain a publicly available document associated with this docket entry. The text of the docket entry is shown above.

Westinghouse Air Brake Technologies Corporation v. Siemens Industry, Inc.
1-17-cv-01687 (DED), 6/19/2018, docket entry 94

EXHIBIT C

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WESTINGHOUSE AIR BRAKE TECHNOLOGIES CORPORATION (d/b/a WABTEC CORPORATION),	)	
Plaintiff,	)	
v.	)	C.A. No. 17-1687 (LPS) (CJB)
SIEMENS INDUSTRY, INC.,	)	**EXPEDITED CONSIDERATION REQUESTED**
Defendant.	)	

LETTER TO THE HONORABLE LEONARD P. STARK FROM KAREN JACOBS REGARDING SIEMENS INDUSTRY, INC.'S MOTION TO STRIKE OR, IN THE ALTERNATIVE, FOR LEAVE TO FILE A SUR-REPLY AND TO EXTEND HEARING DATE

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June 18, 2018

Dear Chief Judge Stark:

Wabtec filed a purported "reply" brief in support of its preliminary injunction motion (D.I. 88) with over 2,000 pages in declarations and exhibits. Less than three weeks before the hearing scheduled for July 3, Wabtec's voluminous reply introduces for the *first time*:

- a declaration from a new expert opining on the validity of the '463 Patent (D.I. 91), with corresponding arguments in the brief;
- new irreparable harm evidence and arguments; *and*
- entire transcripts of 10 depositions not cited in the opening brief.

Wabtec's "trial by ambush" strategy violates the Federal Rules' requirement that "[a]ny affidavit supporting a motion must be served with the motion" (Fed. R. Civ. P. 6(c)(2)), and this Court's mandate that"[t]he party filing the opening brief shall not reserve material for the reply brief which should have been included in a full and fair opening brief." D. Del. LR 7.1.3(c)(2). Siemens therefore moves this Court—under Procedures Order (D.I. 8) and Fed. R. Civ. P. 37—to:

(1) Strike Wabtec's new expert report and new arguments in the reply brief, ***or in the alternative,*** grant Siemens a deposition of the new expert, a sur-reply, and a brief postponement of the PI hearing to afford adequate time for the former.

Siemens further moves this Court to:

(2) Strike the declaration of Timothy Wesley (D.I. 52), and reliance on it in the opening brief (D.I. 49) and in Mr. Bourg's declaration (D.I. 51) and grant Siemens the right to sur-reply to address Wabtec's new irreparable harm arguments; and

(3) Grant Siemens the right to file a sur-reply to address or rebut the new deposition testimony Wabtec submitted for the first time in its reply.

Given the hearing date of July 3, 2018, Siemens respectfully requests consideration of this motion be expedited and that Wabtec have two days to respond, followed by Siemens' reply in two days.[1]

I. Siemens Moves to Strike Wabtec's New Invalidity Expert Report or, in the Alternative, to Conduct Discovery, File a Sur-Reply, and Postpone the Hearing.

Wabtec's reply for the first time introduces an expert declaration on validity from a previously undisclosed expert (Frank Wilson). But unlike most PI cases, Wabtec knew all the asserted prior art references and combinations on which Siemens relies six months before filing its opening brief.[2] (*See* D.I. 49 at 16-17). Wabtec knew when it filed its PI motion that it was obligated

[1] Siemens did not file this motion before today because until Friday morning, June 15, the parties were largely in agreement on the proposed alternative relief (*see* Ex. A, 6/14/18 email from S. Caponi), and the parties had called the Court to check on the Court's availability to reschedule the PI hearing on or about August 1, 2018. Less than 24 hours later—after a meet and confer on an unrelated issue—Wabtec reneged on this tentative agreement and insisted on proceeding with the hearing on July 3, 2018.

[2] Siemens' opposition included a Declaration of John Loud (D.I. 80) opining on the invalidity of the '463 Patent, but all the references he discusses were disclosed (and charted) in Siemens' invalidity contentions.

to address Siemens' invalidity challenges to meet its burden of showing a likelihood of success.[3] *See*, *e.g.*, *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1350 (Fed. Cir. 2001). Nonetheless, Wabtec deliberately chose to save its arguments and expert testimony until its reply brief, in clear violation of Fed. R. Civ. P. 6(c)(2) and this Court's D. Del. LR 7.1.3(c)(2).

Wabtec's gamesmanship materially prejudices Siemens' ability to oppose the PI motion. As noted in Siemens' opposition brief, Wabtec's hide-the-ball tactics kept Siemens in the dark about Wabtec's positions until after Siemens filed its opposition brief. (D.I. 78 at 19). Wabtec should not be allowed to submit a new expert declaration addressing for the first time the invalidity defenses of which it was already aware when it filed its motion, leaving Siemens without a substantive response to those challenges. (*Id.* at n.8). Accordingly, Mr. Wilson's new expert report and the new arguments contained in the reply should be stricken. *See, e.g.*, *Lab.Skin Care, Inc. v. Ltd. Brands, Inc.*, 757 F. Supp. 2d. 431, 437-38 (D. Del. 2010) (precluding new declaration and evidence in a reply brief); *Praxair, Inc. v. ATMI, Inc.*, 231 F.R.D. 457, 463-64 (D. Del. 2005) (striking newly submitted expert opinions because other party did not have sufficient time for rebuttal discovery).

In the alternative, Siemens moves for leave to depose Mr. Wilson and to file a sur-reply, and for a brief postponement of the PI hearing to allow Siemens reasonable time to address the new evidence and arguments raised in Wabtec's reply brief.[4] Wabtec does not oppose the deposition or sur-reply, so long as Siemens completes both before the July 3 hearing. Wabtec's proposal is untenable, however, and would be extremely prejudicial to both Siemens and the Court. *See Socket Mobile, Inc. v. Cognex Corp.*, 2017 WL 3575582, at *5 (D. Del. Aug. 18, 2017).

This Court's schedule contemplated three weeks after Wabtec's reply for both parties and the Court to prepare for the hearing after discovery was completed. (D.I. 59.) Siemens should not be forced to review Wabtec's new 2,000-page filing, take the new expert's deposition, write a sur-reply, **and** prepare for a hearing that now includes cross-examination of a second technical expert (in addition to Wabtec's infringement expert and a corporate witness), while also preparing Siemens' expert witness to rebut the new expert report. Siemens would have to accomplish all of this within **15 days from today**. It would be unjust to consider enjoining the sale of Siemens's products on a record on which Siemens has not had sufficient opportunity to present contrary arguments or testimony and where the Court will not have sufficient time to consider such arguments.

Notably, Wabtec implicitly recognized the need for a surreply and the impracticality of the schedule when it tentatively agreed to move the hearing date just the day before, and it cannot reasonably claim prejudice by postponing the hearing a few weeks considering its delay in filing the original motion.

Should this Court not strike Wabtec's new arguments and evidence, Siemens proposes the following schedule:

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[3] Wabtec filed the cover pleading to Siemens' contentions, but chose only to reference the non-prior art invalidity contentions discussed therein. (*See* D.I. 49 at 16-17 and Ex. O.)

[4] This Court "may grant leave to file a sur-reply if it responds to new evidence, facts, or arguments." *St. Clair Intellectual Prop. Consultants, Inc. v. Samsung Elecs. Co.*, 291 F.R.D. 75, 80 (D. Del. 2013).

- deposition of the new expert during the last week of June;
- a sur-reply up to 15 pages due July 17;
- joint letters on July 20;
- prehearing conference on July 24; and
- the PI hearing on or about August 1,to the extent available on the Court's calendar.

II. Siemens Moves to Strike the Declaration of Timothy Wesley and its New Irreparable Harm Arguments or, in the Alternative, to File a Sur-Reply.

In its opening brief, Wabtec's irreparable harm was based at least in part on an inaccurate and exaggerated number of OBUs that Wabtec's employee, Mr. Wesley, claimed that Siemens had purportedly sold. (*See* D.I. 49 at 6.) Despite acknowledging during that Mr. Wesley's declaration was wholly "inaccurate," Wabtec did not withdraw it, nor inform this Court that several factual allegations in its opening brief and in the Bourg Declaration submitted were therefore also inaccurate. Instead, Wabtec now states it "is no longer relying on" this declaration, (D.I. 88 at 9, n.6), but as Siemens' predicted in its opposition (*see* D.I. 79 at n. 4), Wabtec has now tried to introduce new irreparable harm arguments to which Siemens has had no opportunity to respond. D. Del. LR 7.1.2(c)(2).

Siemens thus requests that the Wesley declaration and corresponding parts of Wabtec's opening brief and Mr. Bourg's Declaration (D.I. 51 at ¶¶ 36-38) be stricken. Wabtec attempts to rectify its irreparable harm argument in its reply with new evidence and arguments (*id.* at 9-10, 11-13), should be stricken as well or, in the alternative, Siemens requests an opportunity to sur-reply.

III. Siemens Moves for Leave to File a Sur-Reply to Address Wabtec's Arguments Based on New Testimony.

Wabtec included the entirety of 10 deposition transcripts as exhibits to its reply. (*See* D.I. 88, Exs. P, Q, T, U, Z, AA, BB, CC, FF and LL.) Not only is the filing of entire deposition transcripts overly inclusive, it also obfuscates Siemens' and the Court's ability to know what testimony Wabtec relies on or plans to offer at the hearing. Siemens requests the opportunity to address the new testimony relied on by Wabtec and to submit new testimony not available when Siemens filed its opposition to the PI in a sur-reply. Wabtec does not oppose this request.

Respectfully,

/s/ Karen Jacobs

Karen Jacobs (#2881)

cc: All Counsel of Record (via electronic mail)

EXHIBIT D

ORAL ORDER: Having reviewed Plaintiff's motion for a temporary restraining order ("TRO") and preliminary injunction ("PI") (D.I. 139), the accompanying opening brief (D.I. 140), and Plaintiff's letter requesting expedited briefing (D.I. 141), as well as Defendants' letter opposing expedited briefing (D.I. 143), IT IS HEREBY ORDERED that Plaintiff's request for expedited consideration of its motion is GRANTED. The parties shall proceed as follows: (i) no later than tomorrow, December 8, at 10:00 a.m., Defendants shall file a letter brief of no more than five single-spaced pages outlining the bases for their opposition to Plaintiff's request for a TRO and/or PI; (ii) no later than December 8 at 2:00 p.m., Plaintiff may file a reply letter brief of no more than two single-spaced pages; and (iii) no later than December 8 at 6:00 p.m., each side shall submit a letter brief, not to exceed five single-spaced pages, addressing the following questions: (a) what role did any defendant play in initiating, participating in, and/or requesting relief from Amazon; (b) if the Court grants Plaintiff's motion and directs Defendants to take actions with respect to Amazon, what likelihood is there that Amazon will respond by again offering Plaintiff's product; (c) if the Court does not find a likelihood that Plaintiff will succeed on the merits, but is concerned that Defendants may be attempting to "circumvent[] the legal system and engage[] in a self-help remedy, instead of letting this Court resolve the parties' dispute pending before this Court" (D.I. 140 at 1), what, if any, relief can the Court provide Plaintiff; (d) should the Court invite Amazon to provide its views on the resolution of the pending motion; and (e) has any court addressed the interplay between Amazon's Utility Patent Neutral Evaluation and ongoing litigation? IT IS FURTHER ORDERED that the Court will hold a teleconference to discuss the parties' submissions on Thursday, December 9 at 9:45 a.m. Plaintiff shall initiate the call to 302-573-4571. ORDERED by Judge Leonard P. Stark on 12/7/21. (ntl) (Entered: 12/07/2021)

EIS Inc. v. IntiHealth Ger GmbH et al
1-19-cv-01227 (DDE), 12/7/2021, docket entry 145

EXHIBIT E

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

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December 6, 2021

The Honorable Leonard P. Stark
United States District Court
for the District of Delaware
844 North King Street
Wilmington, DE 19801

VIA ELECTRONIC FILING

Re: *EIS, Inc. v. WOW Tech International GmbH, et al.*
C.A. No. 19-1227 (LPS)

Dear Judge Stark:

We represent Plaintiff EIS, Inc. ("EIS"), in this action. EIS filed a motion for a temporary restraining order and preliminary injunction late on Friday night, December 3. D.I. 139-40. The motion relates to arrangements Defendants made to have EIS's products taken down from Amazon.com based on charges of infringement of one of the patents in this case just after the Thanksgiving weekend during the busiest shopping season of the year. Defendants did not advise EIS of its proceedings with Amazon. Amazon informed EIS of the take down last week.

On Friday, before filing the motion, we communicated with Defendants' counsel three times about the forthcoming motion and a briefing schedule. Although they declined to get on the phone with us, they responded by email. As to the motion, Defendants' counsel stated that the Defendants never agreed "that the District of Delaware has the sole and exclusive jurisdiction over all disputes between the parties." Although this Court may not have jurisdiction over everything, it certainly has jurisdiction over the infringement and unfair competition issues in this case. As to a briefing schedule, they responded that Defendants "would decid[e] for [them]selves the urgency" of the motion and "would be opposed to an expedited briefing schedule."

Under the circumstances, and due to the irreparable harm to EIS currently occurring and December being a busy sales month, EIS requests an expedited briefing schedule and hearing on its motion. We are available for a telephone conference today or tomorrow if Your Honor has time to hear us.

Respectfully,

/s/ Jack B. Blumenfeld

Jack B. Blumenfeld (#1014)

JBB/bac

cc: All Counsel of Record (via electronic mail)

EXHIBIT F

IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

- - -

ASTRAZENECA PHARMACEUTICALS LP, Plaintiff,	:	CIVIL ACTION
v	:	
NORRIS COCHRAN, in his official capacity as Acting Secretary of the U.S. Department of Health and Human Services; DAN BARRY, in his official capacity as Acting Secretary of the U.S. Department of Health and Human Services; DIANA ESPINOSA, in her official capacity as Acting Administrator of the U.S. Department of Health and Human Services; U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES; and HEALTH RESOURCES AND SERVICES ADMINISTRATION, Defendants.	:	NO. 21-27-LPS

- - -

Wilmington, Delaware
Friday, February 19, 2021
Telephonic Oral Argument

- - -

BEFORE: HONORABLE LEONARD P. STARK, Chief Judge

APPEARANCES:

- - -

McCARTER & ENGLISH, LLP
BY: ALEXANDRA M. JOYCE, ESQ.

and

ARNOLD & PORTER KAY SCHOLER, LLP
BY: ALLON KEDEM, ESQ., and
JEFFREY L. HANDWERKER, ESQ.
(Washington, District of Columbia)

Counsel for Plaintiff

Brian P. Gaffigan
Official Court Reporter

APPEARANCES: (Continued)

U.S. DEPARTMENT OF JUSTICE
BY: RACHAEL L. WESTMORELAND, ESQ.
Trial Attorney
(Washington, District of Columbia)

Counsel for Defendants

- oOo -

P R O C E E D I N G S

(REPORTER'S NOTE: The following telephone conference was held remotely, beginning at 4:33 p.m.)

THE COURT: Good afternoon, everybody. This is Judge Stark. Who is there for the plaintiff, please?

MS. JOYCE: Good afternoon, Your Honor. This is Alexander Joyce from McCarter & English on behalf of plaintiff AstraZeneca. And I'm joined by Allon Kedem, Jeffery Handwerker, both from Arnold & Porter, as well as Danelco Moxey, who is our client representative.

THE COURT: Okay. Thank you very much. Who is there for the defendants, please?

MS. WESTMORELAND: Good afternoon, Your Honor. This is Rachel Westmoreland from the U.S. Department of Justice on behalf of defendants.

THE COURT: Okay. Thank you. And my court reporter, of course, is on the line. And for the record, it is our case of AstraZeneca Pharmaceuticals LP versus Norris Cochran, et al. It is our Civil Action No. 21-27-LPS. And this is the time I set as a status conference to talk about where this case is and some thoughts about how it should perhaps proceed.

Let me start by hearing the -- I've read, of course, the submissions that had been made today. Thank you

for those. But let me start by hearing from the plaintiff as to what you're proposing that I do and why.

MR. KEDEM: Thank you, Your Honor. This is Allon Kedem from Arnold & Porter from AstraZeneca. We know how busy you are and appreciate you acting so quickly on our motion.

Subject to the Court's direction, I'd like to briefly explain our request for expedition and where we hope to go from here.

In light of the imminent harm that AstraZeneca faces, we're seeking preliminary relief to preserve the status quo until our claims can be heard or, in the alternative, briefing on a schedule allowing this Court to move as expeditiously as possible so that the issue can be decided before the advisory opinion is used to cause us harm that can't later be fixed through litigation.

We moved for --

THE COURT: Let me, let me stop you there, Mr. Kedem.

So as I understand it, the alleged irreparable harm is principally focused on when an ADR process I guess concludes? Help me understand what the irreparable harm is pegged to and what is your best estimate as to when that date will arrive.

MR. KEDEM: Sure, Your Honor.

In the ADR proceedings, petitions have been filed seeking orders forcing AstraZeneca to abandon its contract pharmacy policy. And, notably, there had been petitions that had been filed seeking preliminary injunctive relief, meaning they're requesting an injunction before the proceeding even concludes.

We are frankly somewhat in the dark about when that will occur. The petitions have been filed, and the proceedings could start at any time.

It's possible that the government has more information about that than we do. If the government would be willing to stipulate that any sort of order of that type won't issue before a date certain or until you have had a chance to rule, we would be fine with that, but we have no way to know when that kind of order either as a preliminary matter or at the conclusion of an ADR proceeding is likely to come.

THE COURT: Okay. Well, that is helpful. And I will come back to you. I do want to hear more from you, but I'd like to hear then from Ms. Westmoreland on that point principally because I'm trying to figure out how urgent this is, and if the main point of urgency from the plaintiff's perspective is the status of any of these ADR procedures, what, if anything, can the government tell us about the pace at which those are going to move.

MS. WESTMORELAND: Your Honor, I don't have a sort of a date certain to give you or even really a time frame as to how those will move forward, but I will note that the outcome of the ADR proceeding is an agency action that can be reviewed in District Court. And so the government's position is that plaintiff should raise their sort of version of the statutory interpretation in that proceeding which will then eventually be reviewable.

And the idea that the advisory opinion is going to cause plaintiff harm in the ADR proceeding is a little bit misguided as the statutory interpretation that is set out in the former general counsel's views in the advisory opinion have been a long standing position of the agency.

And so the government's position is that there is no emergency based on the advisory opinion with or without the ADR proceedings and that plaintiff should take the opportunity to seek review of any ADR proceeding at the end of those proceedings.

THE COURT: Okay. Thank you for that.

Mr. Kedem, why don't you respond to that and then pick up with whatever else you wanted to address.

MR. KEDEM: Ms. Westmoreland raises what I take to be an exhaustion argument and final agency action argument, and we have responses to those arguments, but I think the more basic point is these are threshold legal

defenses that the government is free to assert in expedited briefing and they can be decided alongside the merits.

There is nothing that is going to happen in the ADR proceedings that will change the validity of those defenses, nor has the government suggested that there would be any discovery or other factual issues. This is a legal question about the meaning of the statute.

And we are not trying to cut off the government's right to argue these defenses or any other defense it wants. We're simply asking to tee the case up for resolution before the imminent harm piles up against us.

And let me just very briefly, if I may, summarize the irreparable harm that AstraZeneca faces now as a result of the unlawful advisory opinion.

Because of these ADR petitions, based on the opinion, AstraZeneca faces an order from the agency directing it to abandon its contract pharmacy policy. You have before you the Caprisecca declaration from AstraZeneca's Executive Director with oversight over the 340B program. In it, she explains that millions of dollars in duplicate discounts were going to contract pharmacies like CVS and Walgreens without any way for AstraZeneca even to identify when and where it was happening, much less to stop it.

In fact, when a different manufacturer, Sanofi,

tried to get the data it would need to stop these double discounts, the agency said that doing so was yet another violation of the 340B statute. So the government has put us between a rock and a hard place. The result is that shutting down AstraZeneca's policy as these ADR petitions threaten to do would mean millions and potentially tens of millions of dollars would be lost to contract pharmacies with no way to stop it or get these funds back later through litigation, and that is on top of the reputational harm and harm to business relationship.

That AstraZeneca is already suffering from covered entities who point to the advisory opinion to say that we are acting illegally. In one, case a covered entity even instructed its pharmacies to completely stop giving AstraZeneca's drugs to its patients even though our policy would allow use of one contract pharmacy.

And, finally, our P.I. motion also details the constitutional harms from being forced to proceed in an unlawful administrative proceeding in violation of the appointments clause in Article III.

So our goal is to avoid these imminent harms. But we are open to any reasonable modification of our proposed schedule by the government. And, you know, last week we thought we and the government could reach an understanding to do just that. But, again, if the government is

not willing to stipulate that there won't be an order in the ADR proceeding, directing us to abandon our policy either on a preliminary or a final basis, then we need to move forward as quickly as possible to head off these harms.

THE COURT: So it sounds at least at the moment like they're not willing to stipulate to that. Let's assume that that is true. Help me understand how the irreparable harm is still present in your view even though you have the right to seek District Court review at end of that ADR process.

MR. KEDEM: Sure. So let's say, Your Honor, that get a ruling from the ADR proceeding or the agency either on a preliminary basis or after the ADR proceeding is concluded, telling us we have to abandon our contract pharmacy policy. As soon as we go back to the pre-existing policy, we are losing millions and potentially tens of millions of dollars that we have no way to identify, no way to know where they're going and therefore, as far as we could tell, no way to get them back later, and we may eventually win.

THE COURT: Sorry. Right. Implicitly, you're saying if the result of the ADR process is a decision that you need to abandon the new policy, you're saying you will have to do that at that point or I guess the question is could you not get some interim relief, move for a

preliminary injunction at that point to maybe ask a court to let you stick with your policy while the court is now reviewing the result of the ADR process? Is something like that potentially a way to alleviate the potential irreparable harm to your client?

MR. KEDEM: Well, Your Honor, I suppose we could seek a TRO on an even more expedited basis than what we're talking about here. I think it's worth emphasizing though that the ADR proceeding, there is no drama about what its result is going to be, the agency has already made crystal clear. So it would essentially be futile, and we would lose all that time, then be forced to rush back into federal court and try and get a ruling, I don't know, in a matter of days or weeks on the very same legal issue that is entirely independent of anything that actually happens in the ADR proceeding, which again the agency has already signalled that it thinks AstraZeneca's policy is inconsistent with the statute.

So we think expedited briefing, if not a preliminary injunction, is a much better way to address that issue. And, again, the government, to the extent it has any legal defenses, saying that we should exhaust or there is no final agency action, it would be perfectly free to raise those defenses at any time.

THE COURT: Under your alternative where we

expedite and go right to summary judgment briefing, you would not, you would not request a preliminary injunction in that context? And the defendant, what would happen to their legal defenses? Would you propose a cross motion for summary judgment or would they still have a chance to file a motion to dismiss under your proposed scenario?

MR. KEDEM: We would be comfortable proceeding on the expedited briefing schedule that we've proposed or something like it as an alternative to ruling on the P.I. motion. And we have proposed a schedule that allows for the government to cross move on any of its defenses. And, you know, we don't want to jam the government up. If it has reasonable modifications that are necessary, we are open to anything along those lines.

But what we don't want is essentially an indefinite hiatus in federal court while the ADR proceeding happens and then to be faced with a potential of a potentially disastrous order that it would take quite a bit of time to get reversed, and in the meanwhile millions of dollars are going out the door with no way to know where or how to get them back in addition to all of the constitutional and reputational harms that we have also identified.

THE COURT: There is reference in the papers to a number of other cases around the country. In your view,

did those cases, any of them present the identical issues that you are putting in front of me or only similar issues? And regardless of the answer to that, are you asking me to move at a different pace than those other courts? And, if so, why?

MR. KEDEM: Your Honor, my understanding, and Ms. Westmoreland can correct me if I'm wrong, is that there are eight suits originally about the 340B program: One has already been dismissed and two have been stayed. Of the remaining five suits, this is the only one in which expedited relief is requested on the basis of the advisory opinion. In those other suits, either they're not requesting expedited relief or they're requesting it for a different purpose because they want to challenge the ADR rule, the rule on which the proceeding is based on constitutional bases.

And so we are asking you to move in a relatively expeditious manner as some of those other cases are moving, but as far as we are aware, we are the only ones who are asking for this issue to be teed up on the advisory opinion itself.

THE COURT: Okay. I'm sure we'll come back to you, but, Ms. Westmoreland, please respond as you wish and point out whatever else you think I should know.

MS. WESTMORELAND: Sure. Thank you, Your Honor.

I first want to start by talking about plaintiff's purported irreparable harm.

So to the extent that they're talking about harm coming from the ADR process and the application of the agency's interpretation of the statute, I want to point out that that ADR process is statutorily required. That rule was issued pursuant to statute.

I also want to point out that this has been the agency's position for a very long time, and that until last summer and early fall, plaintiff was complying or appeared to share the agency's position on the number of contract pharmacies that a covered entity could work with. And so this sort of emergency that has arisen is because of plaintiff's change in position, not because the agency carried out its statutory obligation to set forth the ADR process in a rule.

And with respect to the purported constitutional harm, those relate to the ADR tribunal itself, which is not something plaintiff has chosen to challenge in this case.

I also -- as far as the sort of indefinite hiatus that Mr. Kedem refers to, that is certainly not what the government is seeking. The government is seeking an opportunity to set forth its positions on threshold and jurisdictional issues in a motion to dismiss just a few days after the deadline would come for the government to file a

responsive pleading in this manner.

And I also just want to take the opportunity to clear up something that plaintiff raised in their replies. They sort of state that the government proposed this expedited briefing schedule and then abruptly changed their position, and that is simply just not what happened.

This was plaintiff's idea, and the government spoke to our clients about whether this is something that would work with the agency. And institutionally both for the agency and for the government, it is important to have the opportunity to address the threshold and jurisdictional issues that come up before a case proceeds to a posture where the government would receive a judgment on the merits of that case.

THE COURT: All right. Well, let me ask you a little bit more about that.

I guess what the government is saying is your preference is that I make you respond to the preliminary injunction motion on a schedule maybe along the lines of what you have proposed in your papers and fully brief the motion to dismiss and then I guess determine a schedule for going forward on the merits only after we see if the case survives the motion to dismiss. That is your preference; right?

MS. WESTMORELAND: That's correct, Your Honor.

THE COURT: And I guess what I'm struggling with on that is -- I mean deciding a preliminary injunction motion and thinking about issues like irreparable harm and balance of harm, public interest, that may not be something we have to do, right? It may not be something we have to do because maybe you are going to win on one of your legal defenses on the motion to dismiss, but maybe you are going to lose on those, and then we're going to get to the merits anyway, and the plaintiff isn't going to have to show those things.

So I'm just sort of thinking out loud. Is there, is there merit in considering -- because I take your point about the distinction between risking a judgment on the merits and having your legal defenses, and you cited cases, of course, where it is normally the standard procedure that you would get to have a motion dismiss before summary judgment, but here I just, I wonder if it is worth exploring, could you, you know, could we simultaneously brief summary judgment and a motion to dismiss? And if you win on the -- you know, the motion to dismiss is obviously part of your defense on the merits to the summary judgment motion, but it is also your affirmative legal defense.

I'm just, I'm looking to see if there is an efficient way we can brief what needs to be briefed, decide what needs to be decided, not waste everybody's time with

things that don't have to be decided, and then think about how quickly this can be done.

Should I be thinking in that way at all, Ms. Westmoreland, or should I not?

MS. WESTMORELAND: Well, Your Honor, we certainly want to, you know, find something that is efficient for everyone involved, including the Court. But from the government's perspective, though, there are other factors in sort of the P.I. here.

It's still a very different posture as far as the defense of the merits of the claim. And the government does not want to sort of put the merits of the claim before what it considers to be extremely strong threshold arguments in this case.

So the government's strong preference is to oppose the motion for preliminary injunction, which we, of course, have strong arguments to oppose, and then also move to dismiss on the threshold jurisdictional issues before we reach briefing on the merits of the claims.

THE COURT: There are all these other cases. Can you add anything to what has been outlined for me about the status of those other cases? And, in particular, is this the only one where there is a request for expedited treatment? If so, do you oppose it on that ground as well?

MS. WESTMORELAND: Well, Your Honor, there are

five cases that -- well, there are eight cases. There were eight cases total as Mr. Kedem noted. One has been dismissed, two are stayed, and five are active.

There have been motions for preliminary injunctions in two of those cases. But the -- though at least some of the other cases also challenge the advisory opinion, the motions for preliminary injunction that have been filed thus far were specific to the rule that lays out the ADR process.

So to the extent Your Honor is asking about whether there has been a motion to expedite relief on a claim related to the advisory opinion, there has not. However, some of those cases do raise claims related to the advisory opinion.

But talking about those other cases, plaintiff here filed their case on the same day as two of those other cases and certainly has been watching the schedule unfold in those cases, yet it was the last to move for injunctive relief, the only one to move for injunctive relief on this issue, and is now seeking to sort of bolt the resolution of this case on the merits in front of all the other cases.

THE COURT: Right. And what I couldn't necessarily tell, is that one of your arguments against expedition or against preliminary injunction, hey, these issues are being looked at by multiple judges and why should

AstraZeneca go first?

MS. WESTMORELAND: That's true, Your Honor.

THE COURT: All right. Talk just briefly, Ms. Westmoreland, about putting together the record. It seems likes you had some concern in your letter that maybe that is, I don't know, something of a burden in some way, and it seems like part of the response today to that was that I shouldn't, shouldn't credit that as really a problem because these are going to be legal issues anyway. Can you help me on that?

MS. WESTMORELAND: Well, first of all, Your Honor, plaintiff originally proposed a schedule that would allow the government time to compile an administrative record, and then today said an administrative record was unnecessary, so we're a little confused about the flip-flop there. But as we've all sort of acknowledged, there has been no final agency action here and thus no administrative record would even be necessary.

But to the extent that Your Honor orders the government to provide administrative record or we were to lose on a motion to dismiss, it would take time for the agency to determine what the contents of that record should be and put that before the Court and the parties.

THE COURT: All right. Thank you.

Mr. Kedem, what do you want to add?

MR. KEDEM: There are a few points.

First, just on the administrative record. The advisory opinion says that it's based solely on the plain text of the statute. So we don't see what would go in the administrative record, but Ms. Westmoreland is correct, we built in time to the extent that the government says that they would need time to construct one. And, again, we would be willing to make a reasonable adjustment of that if they insisted they needed additional time.

We frankly don't understand why the government would insist on briefing on the preliminary injunction and decision on a preliminary injunction that could be rendered wholly unnecessary by briefing instead on summary judgment where the government would be free to raise the final agency action or any other threshold issue that it wants to raise. Those issues are not jurisdictional but even if they were, those are precisely the type of arguments that routinely get decided on summary judgment, including in 340B action.

One thing we didn't hear from the government is why there would be literally any prejudice to the government from being forced to proceed in the manner that we suggest. Nor do we hear that they can contest the concrete irreparable harm that AstraZeneca is threatened with.

And I just want to add one more, which is that at the conclusion of an administrative proceeding, the

government could also impose civil monetary penalties which could be pretty exorbitant, and it would be hard to be subject to a $5,000 per violation BMP at the end of the proceeding without any irreparable harm.

So, finally, just on the question of whether we've delayed. You know, I don't know if Your Honor wants us to get more into the back and forth and the reasons why we filed when we did, but it's all tied to the irreparable harm that we face from these ADR petitions.

The first one we got notice of was on January 14th, and we got what we thought was a particularly alarming request for a preliminary injunction that we received on January 21st. We then approached the government on February 8th about a P.I.

And so we believe that we have proceeding expeditiously consistent with our need for swift briefing and decision on the merits, which is really what this is all about. The government can get its threshold jurisdictional or non-jurisdictional issues resolved, and we can get a ruling on the merits that will help us avoid these concrete harms if we ultimately prevail in court.

THE COURT: So if I look at your proposed schedule, Mr. Kedem, for the alternative where we expedite but don't do a P.I., if I counted correctly, it seems like it would take the briefing through mid-April, if I counted

correctly, and you have appropriately indicated you are willing to, you know, discuss possibly a little bit more time if the government needs it.

Is that the -- should I confidently, I mean I am putting aside my own interest for the moment. I'm not saying I can make your case my only case, but if I'm just thinking about it from your perspective, would I be thinking I have until late April-May before this becomes a real emergency for your client?

MR. KEDEM: Your Honor, as I said, we're a little bit in the dark about that, but we are prepared as per the schedule that we had proposed to proceed along those lines. And should something happen in the meantime that would require us to reconsider, we could deal with it then, but, you know, this is our best stab at a schedule that is both livable and won't command too much of the Court's or the parties' resources but would allow us to get to the merits in a swift manner that would allow to avoid what we anticipate to be serious harms.

And, you know, as I said, we are willing to make reasonable adjustments as the government or the Court requests.

THE COURT: Okay. Thank you.

Ms. Westmoreland, is there anything you want to add?

MS. WESTMORELAND: Your Honor, I think our positions have been clearly laid out here. And certainly you have our proposal in writing as well.

I would just add if the Court is inclined to resolve this case on an expedited summary judgment schedule, defendants would just like the opportunity to propose an alternative schedule to the one proposed by plaintiff.

THE COURT: Okay. I appreciate that, and I appreciate the input and the help from both sides.

Here is what -- I am leaning towards expediting and getting to the merits and not having to deal with a preliminary injunction, but I have to admit I'm not quite ready to decide that at just this moment.

I will say what would help me be more comfortable, one way or the other, would be to better understand how that approach would prejudice the government if the government really believes that would prejudice them. That is the argument that I think I'm hearing. And also to note what type of schedule the government would propose as a modification to the plaintiff's proposal if I were to say that is the way we're going to go forward.

So I do have an open mind on this. I'm not rejecting the idea of a preliminary injunction motion and a motion to dismiss being briefed either simultaneously or roughly simultaneously with it, but there is a certain

attraction to giving you all the amount of time you need -- the least amount of time you need to fully brief the merits issue and then we have a single hearing after that is all fully briefed and do my best to make a decision on the time frame that you would want.

So here is where we are. It's the end of the week, at least East Coast time. I would -- I'm going to direct that you all spend a little more time Monday just talking to each other about what the schedule would look like if I say that's the direction we're going to go, namely, the merits briefing. And for the government to have another chance to help me understand why that would be unfairly prejudicial to the government to go in that direction.

I'd like to have the results of those discussions in the form of a joint status report that the plaintiff could submit on behalf of both sides. I'd like to have that by the end of the day Monday, but I also don't want to ruin everybody's weekend.

So tell me what you think, Mr. Kedem. Do you want to make that due Monday? And do you have any more questions for me?

MR. KEDEM: Your Honor, we're willing to proceed on those lines or any other that the Court needs in order to reach a decision.

THE COURT: All right. And, Ms. Westmoreland, what do you think?

MS. WESTMORELAND: Your Honor, we're happy to discuss further with plaintiff and also to explain further in writing the government's position.

I'd only ask because it's the end of the week, it's very difficult to get ahold of our agency client on the weekend regardless of DOJ lawyers' schedules on the weekend, so I would just ask that the JSR be due Tuesday, to allow us Monday at least to talk to our clients before we talk to plaintiff.

THE COURT: Okay. That is fine. So that, I am ordering that all that be submitted on Tuesday. And if I need anything further, which I don't think I will, I will let you know shortly after Tuesday. Otherwise, you can expect that we'll have a schedule for how we're going to go forward as soon after I get your submission on Tuesday.

Anything further then before we break, Mr. Kedem?

MR. KEDEM: No, Your Honor.

THE COURT: And Ms. Westmoreland?

MS. WESTMORELAND: Your Honor, I do just want to clarify. Our opposition to plaintiff's motion for preliminary injunction under the local rules would be due next Friday, the 26th. And it does sound like us filing an

opposition on the 26th is one of the options that is sort of under consideration here, but I just want to confirm that we're not going to need to file a P.I. opposition next Friday.

THE COURT: Mr. Kedem, you can state your position. My thinking is I should at least extend the response to the P.I. by at least as many days from now as it takes me to decide if that is the direction we're going, but do you have an objection to that or a different proposal?

MR. KEDEM: No, Your Honor, we would be amenable to that with the understanding I guess that Your Honor anticipates coming to a decision about the schedule Tuesday in any event -- or, I'm sorry, Your Honor, you know, whenever Your Honor can.

THE COURT: Yes, I certainly expect to do it next week. It will probably be not Tuesday because I'm not hearing from you all until Tuesday.

So, Ms. Westmoreland, you can be comfortable that your brief is hereby ordered not due next Friday. It's due, if I'm thinking correctly, a minimum of two business days after that and probably a minimum of at least three business days after that. And we'll just add on however many days it takes from now until when I determine what the schedule is going to be; okay?

MS. WESTMORELAND: Thank you.

THE COURT: All right. Well, thank you all very much. Have a nice weekend. Stay safe. And we'll be in touch next week. Bye-bye.

MS. WESTMORELAND: Thank you, Your Honor.

MR. KEDEM: Thank you.

(Telephone conference ends at 5:09 p.m.)

I hereby certify the foregoing is a true and accurate transcript from my stenographic notes in the proceeding.

/s/ Brian P. Gaffigan
Official Court Reporter
U.S. District Court

EXHIBIT G

CLOSED,APPEAL

U.S. District Court
District of Delaware (Wilmington)
CIVIL DOCKET FOR CASE #: 1:21−cv−00027−LPS

AstraZeneca Pharmaceuticals LP v. Xavier Becerra et al
Assigned to: Judge Leonard P. Stark
Case in other court: Third Circuit, 22−01676
Cause: 05:702 Administrative Procedure Act

Date Filed: 01/12/2021
Date Terminated: 03/11/2022
Jury Demand: None
Nature of Suit: 899 Other Statutes: Administrative Procedures Act/Review or Appeal of Agency Decision
Jurisdiction: Federal Question

Date Filed	#	Docket Text
05/24/2021	71	ORAL ORDER: Having considered the parties' briefing (see D.I. 66, 69, 70), IT IS HEREBY ORDERED that Plaintiff's motion for administrative stay and, in the alternative, for expedition (D.I. 66) is GRANTED IN PART, to the limited extent that the motions hearing set for June 9, 2021 is expedited and RESCHEDULED for Thursday, May 27 beginning at 1:00 p.m. The parties shall provide a joint letter with videoconference information (see D.I. 53) no later than May 25. In all other respects, Plaintiff's motion is DENIED. ORDERED by Judge Leonard P. Stark on 5/24/21. (ntl) (Entered: 05/24/2021)

EXHIBIT H

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2019

Commission file number: 000-28508

AVADEL PHARMACEUTICALS PLC

(Exact name of registrant as specified in its charter)

Ireland	**98-1341933**
State or other jurisdiction of incorporation or organization	**(I.R.S. Employer Identification No.)**
10 Earlsfort Terrace Dublin 2, Ireland D02 T380	**Not Applicable**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: +011-1-485-1200

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol (s)	Name of exchange on which registered
American Depositary Shares*	AVDL	The Nasdaq Global Market
Ordinary Shares, nominal value $0.01 per share**	AVDL	The Nasdaq Global Market

* American Depositary Shares may be evidenced by American Depository Receipts. Each American Depositary Share represents one (1) Ordinary Share.

** Not for trading, but only in connection with the listing of American Depositary Shares. on The Nasdaq Global Market.

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically, every Interactive Data File required to be submitted and pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☒
Non-accelerated filer ☐ Smaller reporting company ☐
Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of voting stock held by non-affiliates of the registrant as of the last business day of the registrant's most recently completed second fiscal quarter was $97,947,088 based on the closing sale price of the registrant's American Depositary Shares as reported by the Nasdaq Global Market on June 28, 2019. Such market value excludes 3,464,274 ordinary shares, $0.01 per share nominal value, held by each officer and director and by shareholders that the registrant concluded were affiliates of the registrant on that date. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

The number of the registrant's ordinary shares, $0.01 per share nominal value, outstanding as of March 10, 2020 was 46,404,432.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of either (a) a definitive proxy statement involving the election of directors or (b) an amendment to this Form 10-K, either of which will be filed within 120 days after December 31, 2019, are incorporated by reference into Part III of this Form 10-K.

Item 8. Financial Statements and Supplementary Data.

AVADEL PHARMACEUTICALS PLC
CONSOLIDATED STATEMENTS OF (LOSS) INCOME
(In thousands, except per share data)

	Years ended December 31,		
	2019	**2018**	**2017**
Revenues:			
Product sales	$ 59,215	$ 101,423	$ 172,841
License revenue	—	1,846	404
Total revenues	59,215	103,269	173,245
Operating expenses:			
Cost of products	12,125	17,516	16,301
Research and development expenses	32,917	39,329	33,418
Selling, general and administrative expenses	30,183	100,359	58,860
Intangible asset amortization	816	6,619	3,659
Changes in fair value of related party contingent consideration	845	(22,731)	(31,040)
Impairment of intangible asset	—	66,087	—
Restructuring costs	6,441	1,016	2,542
Total operating expenses	83,327	208,195	83,740
Operating (loss) income	(24,112)	(104,926)	89,505
Investment and other income, net	1,069	452	2,136
Interest expense	(12,483)	(10,622)	(1,052)
Loss on deconsolidation of subsidiary	(2,678)	—	—
Other (expense) income - changes in fair value of related party payable	(378)	1,899	2,071
(Loss) income before income taxes	(38,582)	(113,197)	92,660
Income tax (benefit) provision	(5,356)	(17,893)	24,389
Net (loss) income	$ (33,226)	$ (95,304)	$ 68,271
Net (loss) income per share - basic	$ (0.89)	$ (2.55)	$ 1.69
Net (loss) income per share - diluted	$ (0.89)	$ (2.55)	$ 1.63
Weighted average number of shares outstanding - basic	37,403	37,325	40,465
Weighted average number of shares outstanding - diluted	37,403	37,325	41,765

See accompanying notes to consolidated financial statements.

EXHIBIT I

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2020

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period _____ to _____

Commission file number: 000-28508

AVADEL PHARMACEUTICALS PLC

(Exact name of registrant as specified in its charter)

Ireland	**98-1341933**
State or other jurisdiction of incorporation or organization	**(I.R.S. Employer Identification No.)**
10 Earlsfort Terrace Dublin 2, Ireland D02 T380	**Not Applicable**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: +011-1-485-1200

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol (s)	Name of exchange on which registered
American Depositary Shares*	AVDL	The Nasdaq Global Market
Ordinary Shares, nominal value $0.01 per share**	AVDL	The Nasdaq Global Market

* American Depositary Shares may be evidenced by American Depository Receipts. Each American Depositary Share represents one (1) Ordinary Share.

** Not for trading, but only in connection with the listing of American Depositary Shares. on The Nasdaq Global Market.

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically, every Interactive Data File required to be submitted and pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☒
Non-accelerated filer ☐ Smaller reporting company ☐
Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of voting stock held by non-affiliates of the registrant as of the last business day of the registrant's most recently completed second fiscal quarter was $466,741,289 based on the closing sale price of the registrant's American Depositary Shares as reported by the Nasdaq Global Market on June 30, 2020. Such market value excludes 364,026 ordinary shares, $0.01 per share nominal value, held by each officer and director and by shareholders that the registrant concluded were affiliates of the registrant on that date. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

The number of the registrant's ordinary shares, $0.01 per share nominal value, outstanding as of March 4, 2021 was 58,465,151.

of these liabilities are recorded in the consolidated statements of income (loss) within operating expenses as changes in fair value of contingent consideration.

Financing-related Royalty Agreements. We were previously a party to two royalty agreements in connection with certain financing arrangements. We elected the fair value option for the measurement of the financing-related contingent consideration payable associated with the royalty agreements with certain Deerfield and Broadfin entities (the "Deerfield and Broadfin Royalty Agreements") (see *Note 13: Contingent Consideration Payable*). Prior to the sale of the Hospital Products on June 30, 2020, the fair value of financing-related royalty agreements was estimated using the same components used to determine the fair value of the acquisition-related contingent consideration noted above, with the exception of cost of products sold. Changes to these components can also have a material impact on our consolidated statements of income (loss) and balance sheets. Changes in the fair value of this liability are recorded in the consolidated statements of income (loss) as other (expense) income - changes in fair value of contingent consideration payable. In connection with the disposition of the Hospital Products on June 30, 2020 as discussed in *Note 4: Disposition of the Hospital Products*, the Deerfield and Broadfin Royalty Agreements were assigned to the Exela Buyer and the Exela Buyer assumed and shall pay, perform, satisfy and discharge the liabilities and obligations of the Company under the Deerfield and Broadfin Royalty Agreements.

Results of Operations

The following is a summary of our financial results (in thousands, except per share amounts):

	Years Ended December 31,		Increase / (Decrease)	
Comparative Statements of Income (Loss):	**2020**	**2019**	**$**	**%**
Product sales	$ 22,334	$ 59,215	$ (36,881)	(62.3)%
Operating expenses:				
Cost of products	5,742	12,125	(6,383)	(52.6)%
Research and development expenses	20,442	32,917	(12,475)	(37.9)%
Selling, general and administrative expenses	32,405	30,183	2,222	7.4 %
Intangible asset amortization	406	816	(410)	(50.2)%
Changes in fair value of contingent consideration	3,327	845	2,482	293.7 %
Gain on sale of Hospital Products	(45,760)	—	(45,760)	(100.0)%
Restructuring (income) costs	(43)	6,441	(6,484)	(100.7)%
Total operating expenses	16,519	83,327	(66,808)	(80.2)%
Operating income (loss)	5,815	(24,112)	29,927	124.1 %
Investment and other (expense) income, net	(832)	1,069	(1,901)	(177.8)%
Interest expense	(12,994)	(12,483)	(511)	(4.1)%
Gain from release of certain liabilities	3,364	—	3,364	100.0 %
Loss on deconsolidation of subsidiary	—	(2,678)	2,678	100.0 %
Other expense - changes in fair value of contingent consideration payable	(435)	(378)	(57)	(15.1)%
Loss before income taxes	(5,082)	(38,582)	33,500	86.8 %
Income tax benefit	(12,110)	(5,356)	(6,754)	(126.1)%
Net income (loss)	$ 7,028	$ (33,226)	$ 40,254	121.2 %
Net income (loss) per share - diluted	$ 0.13	$ (0.89)	$ 1.02	114.6 %

EXHIBIT J

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549
FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the fiscal year ended December 31, 2021

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
For the transition period _____ to _____

Commission file number: 001-37977

AVADEL PHARMACEUTICALS PLC

(Exact name of registrant as specified in its charter)

Ireland	**98-1341933**
State or other jurisdiction of incorporation or organization	**(I.R.S. Employer Identification No.)**
10 Earlsfort Terrace Dublin 2, Ireland D02 T380	**Not Applicable**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: +353-1-901-5201

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol (s)	Name of exchange on which registered
American Depositary Shares*	AVDL	The Nasdaq Global Market
Ordinary Shares, nominal value $0.01 per share**	AVDL	The Nasdaq Global Market

* American Depositary Shares may be evidenced by American Depository Receipts. Each American Depositary Share represents one (1) Ordinary Share.

** Not for trading, but only in connection with the listing of American Depositary Shares. on The Nasdaq Global Market.

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically, every Interactive Data File required to be submitted and pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☒
Non-accelerated filer ☐ Smaller reporting company ☐
Emerging growth company ☐
If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes ☐ No ☒

The aggregate market value of voting stock held by non-affiliates of the registrant as of the last business day of the registrant's most recently completed second fiscal quarter was $390,167,685 based on the closing sale price of the registrant's American Depositary Shares as reported by the Nasdaq Global Market on June 30, 2021. Such market value excludes 513,155 ordinary shares, $0.01 per share nominal value, which may be represented by the registrant's American Depositary Shares, held by each officer and director and by shareholders that the registrant concluded were affiliates of the registrant on that date. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the registrant.

Item 8. Financial Statements and Supplementary Data.

AVADEL PHARMACEUTICALS PLC
CONSOLIDATED STATEMENTS OF (LOSS) INCOME
(In thousands, except per share data)

	Years ended December 31,		
	2021	**2020**	**2019**
Product sales	$ —	$ 22,334	$ 59,215
Operating expenses:			
Cost of products	—	5,742	12,125
Research and development expenses	17,104	20,442	32,917
Selling, general and administrative expenses	68,495	32,405	30,183
Intangible asset amortization	—	406	816
Changes in fair value of contingent consideration	—	3,327	845
Gain on sale of Hospital Products	—	(45,760)	—
Restructuring (income) costs	(53)	(43)	6,441
Total operating expenses	85,546	16,519	83,327
Operating (loss) income	(85,546)	5,815	(24,112)
Investment and other income (expense), net	2,126	(832)	1,069
Interest expense	(9,942)	(12,994)	(12,483)
Gain from release of certain liabilities	217	3,364	—
Loss on deconsolidation of subsidiary	—	—	(2,678)
Other expense - changes in fair value of contingent consideration payable	—	(435)	(378)
Loss before income taxes	(93,145)	(5,082)	(38,582)
Income tax benefit	(15,816)	(12,110)	(5,356)
Net (loss) income	$ (77,329)	$ 7,028	$ (33,226)
Net (loss) income per share - basic	$ (1.32)	$ 0.13	$ (0.89)
Net (loss) income per share - diluted	$ (1.32)	$ 0.13	$ (0.89)
Weighted average number of shares outstanding - basic	58,535	52,996	37,403
Weighted average number of shares outstanding - diluted	58,535	54,941	37,403

See accompanying notes to consolidated financial statements.

EXHIBIT K

U.S. FOOD & DRUG ADMINISTRATION

Avadel CNS Pharmaceuticals, LLC
Attention: Marla Scarola
The Weinberg Group
1129 Twentieth Street NW, Suite 600
Washington, DC 20036

John R. Manthei
Latham & Watkins LLP
555 Eleventh Street, N.W., Suite 1000
Washington, D.C. 20004

Dear Ms. Scarola and Mr. Manthei:

On December 15, 2020, Avadel CNS Pharmaceuticals, LLC (Avadel) submitted a new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Lumryz (sodium oxybate) extended-release oral suspension (FT218). Avadel's NDA 214755 identifies Xyrem (sodium oxybate) oral solution (NDA 021196) as the listed drug relied upon. In its NDA, Avadel submitted a statement under section 505(b)(2)(B) of the FD&C Act (505(b)(2)(B) statement) and 21 CFR 314.50(i)(1)(iii) to U.S. Patent No. 8,731,963 ('963) listed for Xyrem in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book). The Orange Book identifies the '963 patent as a method-of-use patent with the use code U-1110, "METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION."

On September 17, 2021, Avadel made a submission to its NDA that presented arguments in support of its position that its section 505(b)(2)(B) statement to the '963 patent is appropriate.[1] On behalf of Avadel, Latham & Watkins LLP submitted letters dated October 25, 2021 and April 13, 2022 to the Office of the Chief Counsel (OCC) and the Center for Drug Evaluation and Research (CDER) that restated Avadel's arguments regarding its section 505(b)(2)(B) statement to the '963 patent.[2] Your submissions have been referred to me for response. This letter responds to these arguments from Avadel regarding the appropriateness of Avadel's section 505(b)(2)(B) statement to address the '963 patent and constitutes a final decision on the appropriateness of Avadel's section 505(b)(2)(B) statement to address the '963 patent

[1] NDA 214755, Response to Information Request (Module 1.3.5.2) (September 17, 2021).
[2] Letter from John R. Manthei, Latham & Watkins, LLP, re: Lumryz (sodium oxybate) for extended-release oral suspension (NDA 214755), to Elizabeth Dickinson, OCC, FDA (October 25, 2021); Letter from John R. Manthei, Latham & Watkins, LLP, re: Lumryz (sodium oxybate) for extended-release oral suspension (NDA 214755), to Patrizia Cavazzoni, M.D., Director, CDER, FDA (April 13, 2022).

listed for Xyrem in the Orange Book.[3,4] For the reasons set forth below, we have concluded that Avadel is seeking approval of a condition of use that is claimed by the '963 patent, as described by the U-1110 use code, and thus Avadel's proposed section 505(b)(2)(B) statement to address this patent is inappropriate.

I. Legal and Regulatory Background

Under the FD&C Act, an NDA applicant must submit to FDA, among other things, information on any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug.[5] An NDA applicant must submit the patent information to its NDA on Form FDA 3542a.[6] After approval of an NDA (including certain types of supplements to an NDA) but within certain time frames prescribed in the FD&C Act and FDA's implementing regulations, NDA holders must submit required patent information on Form FDA 3542 for listing in the Orange Book.[7] FDA is required to publish patent information submitted under section 505(c) of the FD&C Act and does so in the Orange Book based on the information in the submitted Form FDA 3542. For method-of-use patents, the information submitted by the NDA holder and published by FDA in the Orange Book includes a brief description of the approved method of use claimed by the patent, known as the "use code."[8] FDA has a

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[3] We note that this letter does not address the appropriateness of Avadel's section 505(b)(2)(B) statements to U.S. Patent Nos. 8,772,306; 9,050,302; 9,486,426; 10,864,181; 10,213,400; and 11,253,494 listed for Xyrem in the Orange Book. FDA intends to respond to Avadel on these issues under separate cover.

[4] This letter does not address whether any orphan drug exclusivity (ODE) recognized for Xyrem under NDA 021196 or for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution under NDA 212690 affects the approvability of Avadel's NDA 214755. FDA's general practice is not to make a determination regarding the impact of ODE on the approvability of an application until FDA is otherwise ready to take an approval action on such application. If FDA were to make such a determination prior to the time of approval, it is possible that circumstances could change between the time that FDA makes a determination on the impact of ODE and the time the application is ready for approval (e.g., the orphan exclusivity might expire or there might be additional patents or exclusivities to consider).

[5] Section 505(b)(1) of the FD&C Act (2020); see also 21 CFR 314.53(c)(2)(i). The Orange Book Transparency Act of 2020 (P.L. 116-290) was enacted on January 5, 2021, and amended section 505(b)(1) of the FD&C Act with respect to the submission of patent information to require NDA applicants to file information on each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and "that claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent[,]" or "claims a method of using such drug for which approval is sought or has been granted in the application" (section 505(b)(1)(A)(viii) of the FD&C Act).

[6] See 21 CFR 314.53(c).

[7] See section 505(c)(2) of the FD&C Act and 21 CFR 314.53.

[8] In 2016, FDA codified its longstanding position that the NDA holder's description of the patented method of use required for publication in the Orange Book "must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval" (see "Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule," 81 FR 69580, 69597 (October 6, 2016) (MMA Final Rule) and 21 CFR

ministerial role in listing patent information submitted by an NDA holder for publication in the Orange Book. Therefore, FDA does not review the applicable patent to evaluate the appropriateness of the NDA holder's patent listing or the accuracy of its use codes.

An applicant seeking approval of an NDA submitted pursuant to section 505(b)(2) of the FD&C Act that relies on one or more listed drugs must submit with its NDA an appropriate patent certification or statement with respect to certain patents for such relied-upon listed drugs.[9] In particular, the 505(b)(2) applicant generally must submit to FDA one of four specified certifications regarding the patents for the relied-upon listed drug(s) under section 505(b)(2)(A) of the FD&C Act. If the Orange Book does not list a patent for the relied-upon listed drug(s), the 505(b)(2) applicant must certify that such patent information has not been filed (a paragraph I certification).[10] If the Orange Book does list one or more patents for the relied-upon listed drug(s), with respect to each such listed patent, the 505(b)(2) applicant's patent certification must state one of the following:

- that such patent has expired (a paragraph II certification),
- the date on which such patent will expire (a paragraph III certification), or
- that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted (a paragraph IV certification).[11]

An applicant submitting a paragraph IV certification to a listed patent must provide the NDA holder and each patent owner with notice of its patent certification, including a description of the legal and factual basis for the 505(b)(2) applicant's assertion that the patent is invalid, unenforceable, or not infringed.[12]

The patent certifications described above are not the only way in which a 505(b)(2) applicant may address certain types of patents listed in the Orange Book for a particular listed drug. When a patent is listed as claiming a method of use, a 505(b)(2) applicant that is not seeking approval for the method of use claimed by the listed patent need not file a paragraph III or IV certification for that patent. Instead, the applicant may submit a

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314.53(c)(2)(ii)(P)(*3*)). For example, the regulation requires that "if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product". 21 CFR 314.53(c)(2)(ii)(P)(*3*). See also 21 CFR 314.53(b)(1) ("For patents that claim a method of use, the applicant must submit information only on those patents that claim indications or other conditions of use for which approval is sought or has been granted in the NDA.").

[9] See section 505(b)(2)(A) and (B) of the FD&C Act and 21 CFR 314.50(i)(1)(i)-(iii).

[10] 21 CFR 314.50(i)(1)(i)(A)(*1*). If in the opinion of the 505(b)(2) applicant and to the best of its knowledge there are no patents claiming the drug product, drug substance, or method of use of the drug product for the relied-upon listed drug, the 505(b)(2) applicant must submit to its application a certification stating that opinion. 21 CFR 314.50(i)(1)(ii).

[11] See section 505(b)(2)(A)(ii)-(iv) of the FD&C Act and 21 CFR 314.50(i)(1)(i)(A)(*2*)-(*4*).

[12] See section 505(b)(3) of the FD&C Act and 21 CFR 314.52.

statement acknowledging that a method-of-use patent has been listed for the drug, but stating that the patent at issue does not claim a use for which the applicant is seeking approval.[13] Specifically, section 505(b)(2)(B) of the FD&C Act provides that "if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, [the 505(b)(2) application must contain] a statement that the method of use patent does not claim such a use." This type of statement submitted under section 505(b)(2)(B) of the FD&C Act and 21 CFR 314.50(i)(1)(iii) to address a method-of-use patent is known as a "section 505(b)(2)(B) statement." Submission of such a statement requires the 505(b)(2) applicant to omit from its labeling information covered by the method-of-use patent.[14]

Under FDA's regulations, a 505(b)(2) applicant's submission of a section 505(b)(2)(B) statement would be appropriate when "the labeling for the drug product for which the applicant is seeking approval does not include an indication or other condition of use that is covered by the method-of-use patent."[15] Similarly, FDA's regulations also provide that "[i]f the labeling of the drug product for which the applicant is seeking approval includes an indication or other condition of use that, according to the patent information submitted under section 505(b) or (c) of the Federal Food, Drug, and Cosmetic Act and § 314.53 or in the opinion of the applicant, is claimed by a method-of-use patent, the applicant must submit an applicable [patent] certification…."[16] Although FDA takes a ministerial role in listing patent information in the Orange Book and does not independently evaluate the information provided in the use code in relation to the specific patent at issue, FDA nevertheless regularly evaluates what portions of labeling appropriately correspond to the use code provided and whether a 505(b)(2) application may be approved with labeling that omits information protected by the relevant use code provided. Such determinations fall squarely within the ambit of FDA's scientific expertise.[17]

In evaluating a 505(b)(2) applicant's proposed section 505(b)(2)(B) statement, FDA must determine whether an applicant's proposed labeling is consistent with the applicant's assertion that it is not seeking approval for the protected use described by

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[13] See section 505(b)(2)(B) of the FD&C Act and 21 CFR 314.50(i)(1)(iii).
[14] See 21 CFR 314.50(i)(1)(iii).
[15] See 21 CFR 314.50(i)(1)(iii)(A). The prescribing information is part of FDA-approved labeling for a prescription drug product.
[16] See 21 CFR 314.50(i)(1)(iii)(B).
[17] See Letter from CAPT Jason Woo, Acting Director, Office of Regulatory Operations, Office of Generic Drugs, CDER, to Dexmedetomidine Hydrochloride Injection NDA Holder/ANDA Applicant, re: Docket No. FDA-2014-N-0087 (August 18, 2014) (Precedex Labeling Carve Out Letter) at 8, available at https://www.regulations.gov/document/FDA-2014-N-0087-0025; see also MMA Final Rule, 81 FR 69580 at 69600 ("Although identification of the section(s) and subsection(s) of labeling identified by the NDA holder may assist FDA in exercising its scientific judgment to implement section 505(b)(2)(B) and (j)(2)(A)(viii) of the FD&C Act, FDA is not bound by the section(s) and subsection(s) identified by the NDA holder in section 4.2a of Form FDA 3542 in making its determination. FDA will use its independent scientific judgment to determine which section(s) and/or subsection(s) of labeling contain language that must be carved out based on the use code provided.").

the patent use code. If FDA determines that the labeling proposed does not include the protected use, FDA must also determine whether the proposed product as labeled is safe and effective.

II. Factual Background

A. Xyrem Risk Evaluation and Mitigation Strategy

FDA initially approved Xyrem (NDA 021196) under the restricted distribution provisions of 21 CFR 314 Subpart H, and Xyrem was approved with the Xyrem Risk Management Program to assure safe use of the product (also referred to at the time as the "Xyrem Success Program"). Sodium oxybate, which is a central nervous system (CNS) depressant and Schedule III controlled substance under the Controlled Substances Act (CSA), is associated with the risks of abuse and misuse. Sodium oxybate, the active ingredient of Xyrem, is the sodium salt of gamma-hydroxybutyrate (GHB), which is a Schedule I controlled substance under the CSA. Abuse of GHB either alone or in combination with other CNS depressants is associated with adverse reactions including seizure, respiratory depression, decreases in the level of consciousness, coma, and death. The rapid onset of sedation, coupled with amnesia, particularly when combined with alcohol, has proven to be dangerous for voluntary and involuntary users (e.g., assault victims). Because illicit use and abuse of GHB have been reported, the Xyrem labeling advises physicians to carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of GHB.[18] When used for the treatment of cataplexy or EDS, physicians are advised that Xyrem is contraindicated in combination with alcohol and sedative hypnotics, and the concurrent use of Xyrem with other CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.

Section 505-1 of the FD&C Act establishes FDA's risk evaluation and mitigation strategy (REMS) authority. A REMS is a required risk management strategy that includes one or more elements to ensure that the benefits of a drug outweigh its risks. When Congress passed the FDA Amendments Act (FDAAA) in 2007, which established Section 505-1, it set forth a comprehensive statutory framework that requires a careful balance between the need to evaluate and mitigate the risks of a drug to ensure that its benefits outweigh its risks, and the potential burdens of REMS elements on patient access and the health care delivery system. For drugs previously approved under Subpart H with restricted distribution, like Xyrem, FDAAA established that they were "deemed to have in effect an approved [REMS] under Section 505-1 of the [FD&C] Act," and required the submission of a proposed REMS within 180 days for FDA's review and approval.[19] A REMS for Xyrem was approved by FDA on February 27, 2015.[20]

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[18] See, for example, section 5.2 (Abuse and Misuse) and 9.2 (Abuse) of the Xyrem prescribing information.
[19] See section 909 of FDAAA.
[20] On July 21, 2020, FDA approved NDA 212690 for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution, which is also held by Jazz. Xywav is subject to the same REMS as

The Xyrem REMS requires, among other things, elements to assure safe use (ETASU) to mitigate the risks of serious adverse outcomes resulting from inappropriate prescribing, misuse, abuse, and diversion of Xyrem. Prior to filling a Xyrem prescription, the pharmacy must screen for a patient's concomitant use of sedative-hypnotics and other potentially interacting agents; monitor for inappropriate prescribing, misuse, abuse, and diversion; and notify prescribers when patients are receiving concomitant contraindicated medications or there are signs of potential abuse, misuse, or diversion. In addition, the REMS is designed to mitigate the risks by informing prescribers, pharmacists, and patients of the risk of significant central nervous system and respiratory depression associated with Xyrem; the contraindication of use of Xyrem with sedative-hypnotics and alcohol; the potential for abuse, misuse, and overdose associated with Xyrem; and the safe use, handling, and storage of Xyrem. The Xyrem REMS utilizes (1) a central pharmacy to distribute Xyrem (called the "Central Pharmacy") and (2) a secure and validated database (called the "Central Database") to maintain and track certain patient and prescriber information and uses.[21]

B. Xyrem Listed Patents

The Orange Book currently lists the following unexpired patents[22] under the Xyrem NDA (NDA 021196):

Patent Number	Expiration Date	Use Code	Delist Requested	Submission Date
7,668,730*PED	12/16/2024	U-1110	Yes	
8,731,963*PED	6/17/2023	U-1110		05/30/2014
8,772,306*PED	9/15/2033	U-1532		07/09/2014
9,050,302*PED	9/15/2033	U-1532		07/08/2015
9,486,426*PED	9/15/2033	U-1532		12/06/2016

Xyrem. Since the approval of NDA 212690 for Xywav, this REMS has been known as the "Xywav and Xyrem REMS". See NDA 212690 for Xywav (calcium, magnesium, potassium, and sodium oxybates) oral solution, Approval Letter (July 21, 2020), available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/212690Orig1s000ltr.pdf. For the sake of clarity, this letter generally refers to the "Xyrem REMS" when referring to the REMS required for Xyrem under NDA 021196.

[21] See, e.g., XYWAV and XYREM REMS Document, dated February 2022, at 7 ("Jazz Pharmaceuticals must…[e]stablish and maintain a validated, secure database, called the Central Database, of all REMS participants who have been or are enrolled and/or certified in the XYWAV and XYREM REMS Program. The database must include the following information: prescriber and patient enrollment status, all completed forms, prescription and shipment data as well as dosing, concomitant medications, behavior that raises suspicion of abuse, misuse, or diversion including all alerts and risk management reports.").

[22] As of the date of Avadel's original submission of NDA 214755 for Lumryz (December 15, 2020), the Orange Book also listed several other expired or then-soon-to-be-expired patents under NDA 021196 for Xyrem. In its original NDA submission, Avadel submitted paragraph II certifications to address the expired patents (i.e., U.S. Patent Nos. 7,851,506, 8,263,650, 8,324,275, 8,859,619, 8,952,062, and 9,539,330, which expired on June 22, 2020) and paragraph III certifications to address the then-soon-to-be expired patents (i.e., U.S. Patent Nos. 6,780,889 and 7,262,219, which expired on January 4, 2021). See NDA 214755 (Lumryz (sodium oxybate) for extended-release oral suspension), Patent Certification (Module 1.3) (December 15, 2020).

10,213,400	3/15/2033	U-2499		03/28/2019
10,864,181	3/15/2033	U-1532		01/13/2021
11,253,494	3/15/2033	U-3323 U-3324		3/15/2022
U-1110: METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION U-1532: METHOD OF TREATING EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY PATIENTS WITH SODIUM OXYBATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED U-2499: METHOD OF REDUCING ADVERSE EFFECTS IN PATIENTS SUFFERING FROM EXCESSIVE DAYTIME SLEEPINESS AND/OR CATAPLEXY IN NARCOLEPSY WHO ARE CONCOMITANTLY ADMINISTERED SODIUM OXYBATE AND DIVALPROEX SODIUM U-3323: METHOD OF REDUCING ADVERSE EFFECTS IN PATIENTS WHO ARE CONCOMITANTLY ADMINISTERED A SALT OF GAMMA-HYDROXYBUTYRATE AND DIVALPROEX SODIUM U-3324: METHOD OF TREATING PATIENTS WITH A SALT OF GAMMA-HYDROXYBUTYRATE WHEN DIVALPROEX SODIUM IS CONCOMITANTLY ADMINISTERED				

As discussed further below, the U-1110 use code listed under U.S. Patent Nos. 7,668,730 ('730 patent) and 8,731,963 ('963 patent) describes certain aspects of the Xyrem REMS described in the Xyrem labeling. In the Form FDA 3542 accompanying Jazz's request on March 15, 2011 to update the use code listed for the '730 patent[23] and in the Form FDA 3542 accompanying Jazz's request on May 30, 2014 to list the '963 patent, Jazz identified certain language from the then-approved Xyrem prescribing information related to the Xyrem Success Program[24] as describing the protected U-1110 use, along with all of the information in an attached document entitled "XYREM RISK MANAGEMENT PROGRAM."[25] The version of the Xyrem Risk Management Program highlighted in the Form 3542 for the '730 and '963 patents, was approved by FDA as part of a supplement to the Xyrem NDA on November 18, 2005 and makes reference to

[23] On February 23, 2010, Jazz submitted an initial Form FDA 3542 to request the listing of the '730 patent with the following use code: "A method of distributing sodium oxybate under control of a central pharmacy." On March 15, 2011, Jazz submitted an updated Form FDA 3542 to update the expiration date listed for the '730 patent, as well as revise the use code to "method of treating a patient with a prescription drug using a computer database in a computer system for distribution."

[24] As it relates to the Form FDA 3542 for the '963 patent, the sections of the attached prescribing information that were highlighted by Jazz included statements in the Boxed Warning, Indications and Usage (section 1), Dosage and Administration (section 2), Warnings and Precautions (section 5.3 (including contact information)), Patient Counseling Information (section 17), and Medication Guide. In relation to the updated Form FDA 3542 for the '730 patent, the sections of the attached prescribing information that were highlighted by Jazz included statements in the Boxed Warning, Information for Patients subsection of the Precautions section, contact information, and Medication Guide.

[25] See NDA 021196/S-005 (November 18, 2005). As explained in section II.A, with enactment of FDAAA, Xyrem's Risk Management Program was deemed a REMS, and FDA approved the REMS in 2015.

a "database" and "secure database" used by the "central pharmacy."[26]

III. Discussion

A. *Avadel's Section 505(b)(2)(B) Statement for the '963 Patent with U-1110 Use Code*

In its original NDA submission, Avadel provided a section 505(b)(2)(B) statement to address the '730 patent and '963 patent listed for NDA 021196 for Xyrem in the Orange Book.[27] As noted above, the '963 patent listed for Xyrem is identified as a method-of-use patent with the use code U-1110, "METHOD OF TREATING A PATIENT WITH A PRESCRIPTION DRUG USING A COMPUTER DATABASE IN A COMPUTER SYSTEM FOR DISTRIBUTION." As support for its position that a section 505(b)(2)(B) statement to the '963 patent is appropriate, Avadel asserted the following in its original NDA submission:

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As further support for its position, Avadel provided copies of a patent listing dispute submitted by counsel for Avadel to FDA in 2019 pursuant to 21 CFR 314.53(f)(1) disputing the accuracy of the listing for the '963 patent.[29] The patent listing dispute under 21 CFR 314.53(f)(1) asserted that the remaining claims of the '963 patent do not cover a method of use, but rather a system for mitigating Xyrem's risks, and thus the '963 patent is improperly listed as a method-of-use patent.[30] In response to this patent

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[26] See, e.g., Form FDA 3542, NDA 021196 (May 30, 2014) ('963 patent) at 35-38. The Xyrem Risk Management Program approved as part of NDA 021196/S-005 is identified as "FDA Approved Labeling Text." See NDA 021196/S-005, Approved Labeling (November 18, 2005), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021196s005lbl.pdf.

[27] The Orange Book indicates that the '730 patent has been requested by Jazz to be delisted. A 505(b)(2) applicant is not required to provide or maintain a certification to a patent or patent information that remains listed only for purposes of a first applicant's 180-day exclusivity for its ANDA. See 21 CFR 314.50(i)(6)(ii). Therefore, the discussion in this letter focuses on the '963 patent. As explained below in the Conclusion section, Avadel should withdraw its section 505(b)(2)(B) statement to the '730 patent.

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[29] See Letter from Jeffrey S. Ward to Orange Book Staff, CDER, FDA re: 314.53(f) Patent Listing Dispute – '963 patent (September 24, 2019); see also NDA 214755 (Lumryz (sodium oxybate) for extended-release oral suspension), Patent Certification (Module 1.3) (December 15, 2020) at 2-3.

[30] See Letter from Jeffrey S. Ward to Orange Book Staff, CDER, FDA re: 314.53(f) Patent Listing Dispute – '963 patent (September 24, 2019).

listing dispute, Jazz confirmed the correctness of the description of the approved method of use for Xyrem claimed by the '963 patent and included as the U-1110 use code in the Orange Book.[31]

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B. *Analysis of Section 505(b)(2)(B) Statement for the '963 Patent with U-1110 Use Code*

As noted above, if a 505(b)(2) applicant submits a section 505(b)(2)(B) statement for a particular method-of-use patent, FDA evaluates the labeling for the proposed product and utilizes its independent scientific judgment to determine whether the 505(b)(2) applicant is not seeking approval for the protected use based on the use code submitted by the NDA holder. In evaluating the appropriateness of Avadel's section 505(b)(2)(B) statement for the U-1110 use code listed under the '963 patent, including whether Avadel is seeking approval for a method of use protected by Xyrem's listed patent, FDA relies on the use code provided by Jazz and listed for Xyrem in the Orange Book.[34] For

[31] NDA 021196, Response to Statement of Patent Dispute (Module 1.3.5.1) (October 29, 2019).

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[34] Consistent with its ministerial role, FDA has not evaluated what the '963 patent actually covers or whether the use code published in the Orange Book accurately reflects what is covered by the '963 patent. In addition, FDA is currently reviewing comments in response to a Federal Register Notice seeking comment on, among other things, the appropriateness of listing patents related to an established REMS (see "Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request

the reasons set forth below, we have concluded that Avadel is seeking approval of a condition of use that is claimed by the '963 patent, as described by the U-1110 use code, and thus Avadel's proposed section 505(b)(2)(B) statement to address this patent is inappropriate.

a. U-1110 Use Code Listed for the '963 Patent for Xyrem

The U-1110 use code listed for the '963 patent reads "method of treating a patient with a prescription drug using a computer database in a computer system for distribution." As an initial matter, we have evaluated what specific portions of Xyrem labeling describes the method of use claimed by the U-1110 use code listed for the '963 patent.

In evaluating what portions of labeling appropriately correspond to a listed use code, a review of the use code and relevant prescribing information ordinarily provides the information necessary for FDA to exercise its independent scientific judgment to determine the scope of protected information in the product labeling.[35] The U-1110 use code presents a unique consideration in that the current FDA-approved Xyrem prescribing information (dated September 25, 2020) does not explicitly describe the use of "a computer database in a computer system for distribution" of Xyrem. Rather, the Xyrem prescribing information describes the restricted distribution of Xyrem, by making reference to the Xyrem REMS. For instance, section 5.3 of the Xyrem prescribing information, entitled XYWAV and XYREM REMS, states that "Xyrem is available only through a restricted distribution program"—the Xyrem REMS—and provides a high-level description of the Xyrem REMS program requirements.[36] The Xyrem prescribing information does not provide a complete description of the Xyrem REMS program requirements and therefore review of the Xyrem prescribing information alone is not sufficient in this case to enable FDA to determine what is described by the '963 patent

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for Comments," 85 FR 33169 (June 1, 2020); see also "Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments; Reopening of Comment Period," 86 FR 14450 (March 16, 2021)). FDA is continuing to evaluate whether additional clarity is needed regarding the types of patent information that should be included in, or removed from, the Orange Book, consistent with the existing statutory requirements for patent listing in the FD&C Act. FDA's decision here regarding the '963 patent is not intended to prejudge that effort. Rather, this letter addresses patents with REMS-related use codes because they are currently listed in the Orange Book.

[35] The Form FDA 3542 submitted by the NDA applicant may assist FDA in its review. Here, in its Form FDA 3542 for the listing of the '963 patent, Jazz identified various portions of the Xyrem prescribing information (as it existed at the time) mentioning the Xyrem Success Program, as well as the Xyrem Risk Management Program document, as describing the method of use claimed by the '963 patent. FDA is not bound by the particular labeling identified by the NDA holder in section 4.2a of Form FDA 3542 in making its determination of what specific labeling describes the protected method of use. See MMA Final Rule, 81 FR at 69600. Here, the Xyrem Risk Management Program documents have been revised in the context of FDA's REMS authorities. In addition, Jazz identified almost every aspect of the Xyrem Success Program as being protected by the U-1110 use code, which is not consistent with the more narrow language of the use code pertaining to treating a patient with a prescription drug "using a computer database in a computer system for distribution." Therefore, Jazz's Form FDA 3542 for the '963 patent was not particularly useful in FDA's analysis.

[36] Section 5.3 of the Xyrem prescribing information states: "Xyrem is available only through a restricted distribution program called the XYWAV and XYREM REMS because of the risks of central nervous system depression and abuse and misuse."

as reflected in the U-1110 use code. Under this unique circumstance wherein the Xyrem prescribing information does not explicitly describe the use of "a computer database in a computer system for distribution" of Xyrem and the Xyrem REMS document does describe this use, FDA determined it appropriate to expand its review of the use code beyond the prescribing information to also consider the Xyrem REMS document, which describes the REMS program requirements in detail.[37]

FDA has determined that the current FDA-approved Xyrem REMS document (dated February 2022), and in particular the REMS Requirements section, describes the protected method of use claimed by the U-1110 use code—it describes a method of treating a patient with a prescription drug using a computer database for the distribution of Xyrem. The REMS document describes that Jazz must establish and maintain a "validated, secure database," known as the Central Database, containing information for "all REMS participants who have been or are enrolled and/or certified in the XYWAV and XYREM REMS Program."[38] The REMS document notes that the "database must include the following information: prescriber and patient enrollment status, all completed forms, prescription and shipment data as well as dosing, concomitant medications, behavior that raises suspicion of abuse, misuse, or diversion including all alerts and risk management reports."[39] In addition to describing the type of information contained within the database, the Xyrem REMS document describes how the database is used in the distribution of Xyrem to patients once prescribed by their healthcare provider.[40]

b. Evaluation of Lumryz NDA and U-1110 Use Code

In evaluating the appropriateness of Avadel's proposed 505(b)(2)(B) statement to the '963 patent, we must determine whether Avadel is seeking approval for the protected use described in the U-1110 use code.[41] In conducting this analysis, we have reviewed the proposed Lumryz prescribing information and the proposed Lumryz REMS document.

The proposed Lumryz prescribing information describes that "LUMRYZ is available only through a restricted program under a REMS."[42] Section 5.3 (LUMRYZ REMS Program) of the proposed Lumryz prescribing information provides a high-level description of the REMS program requirements.[43] However, as with the Xyrem prescribing information,

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[37] A REMS document establishes the goals and requirements of the REMS as they relate to the required REMS elements. The REMS Requirements section of a REMS document generally establishes the requirements of the REMS for both the REMS participant(s) and the applicant(s). See FDA's guidance for industry, *Format and Content of a REMS Document* at 4-5. All approved REMS documents are posted on FDA's website.

[38] XYWAV and XYREM REMS Document dated February 2022 at 7. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Xywav_and_Xyrem_2022_02_09_REMS_Document.pdf

[39] Id.

[40] For instance, the pharmacy is required to "[a]ssess the patient's potential for abuse, misuse, and diversion by reviewing the alerts and Risk Management Report history in the Central Database." Id. at 5.

[41] See 21 CFR 314.50(i)(1)(iii).

[42] See section 5.2 (Abuse and Misuse) of the proposed Lumryz prescribing information.

[43] See draft prescribing information included as Appendix A, at 6.

the Lumryz prescribing information does not provide the complete description of all the Lumryz REMS program requirements. REDACTED

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The U-1110 use code covers a "method of treating a patient with a prescription drug using a computer database in a computer system for distribution." As described above, the Xyrem REMS document notes that Jazz uses a computer database as part of the Xyrem REMS for distribution of its product. Consistent with its ministerial role, FDA relies on the language of the use code. On its face, the U-1110 use code applies to the use of "*a* computer database" (emphasis added) in a computer system for distribution of

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REDACTED As a result, we conclude that Avadel's proposed section 505(b)(2)(B) statement to address the '963 patent for the U-1110 use code is inappropriate.[45] Avadel must submit an appropriate patent certification to address the '963 patent.

c. Response to Avadel's Arguments in Support of Section 505(b)(2)(B) Statement for the '963 Patent

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[45] See 21 CFR 314.50(i)(1)(iii)(B).

As noted above, Avadel has proposed certain arguments in support of its position that its proposed section 505(b)(2)(B) statement is appropriate to address the U-1110 use code under the '963 patent, including in its September 17, 2021, response to FDA's September 10, 2021, information request.[46] These arguments are addressed below.

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[49] See 21 CFR 314.53(f)(1)(i)(B)(*1*) ("If the NDA holder confirms the correctness of the patent information, provides the narrative description required by paragraph (f)(1)(i)(B) of this section, and includes the signed verification required by paragraph (c)(2)(ii)(R) of this section within 30 days of the date on which the Agency sends the statement of dispute, the Agency will not change the patent information in the Orange Book."). We note that if an NDA holder provides a timely response to a patent listing dispute and a 505(b)(2) (or ANDA) applicant disagrees with the NDA holder's response to the patent listing dispute (or disagrees with the use code), the 505(b)(2) (or ANDA) applicant may submit a paragraph IV certification to challenge the method-of-use patent and assert a counterclaim in the context of an infringement action or pursue a declaratory judgment action, as appropriate, to obtain patent certainty (MMA Final Rule, 81 FR at 69606; see also section 505(c)(3)(D)(i) and (ii) of the FD&C Act). Here, Jazz initiated patent infringement litigation against Avadel regarding the '963 patent (among other patents), and in this litigation, Avadel asserted a counterclaim seeking the delisting of the '963 patent from the Orange Book. See *Jazz Pharmaceuticals, Inc. v. Avadel Pharmaceuticals PLC*, Civil Action No. 1:21-cv-00691, Doc. 21 (D. Del. Filed July 23, 2021). It is our understanding that this litigation is ongoing. See *Jazz Pharmaceuticals, Inc. v. Avadel Pharmaceuticals PLC*, Civil Action No. 1:21-cv-00691, Doc. 55 (D. Del. Filed October 19, 2021) (court memorandum opinion denying Avadel's motion for partial judgment on the pleadings with respect to its counterclaim to delist the '963 patent).

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[51] See FDA's analysis of the use code in section III.B.a.

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[53] Id.

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[55] See FDA's analysis of the use code in section III.B.b.

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IV. Conclusion

For the reasons set forth above, FDA concludes that Avadel's proposed section 505(b)(2)(B) statement to address the '963 patent for the U-1110 use code is inappropriate. Therefore, Avadel must provide an appropriate patent certification under 21 CFR 314.50(i)(1)(i) to address the '963 patent.

We remind you that if you elect to submit a paragraph IV certification (21 CFR 314.50(i)(1)(i)(A)(4)) with respect to the '963 patent, the certification must be accompanied by a statement that you will comply with the requirements under § 314.52(a) with respect to providing a notice to each owner of the patent or its representative and to the NDA holder for the drug product that is claimed by the patent or a use of which is claimed by the patent and with the requirements under § 314.52(b) with respect to sending the notice and under § 314.52(c) with respect to the content of the notice. You also would be required to amend your application to include documentation of timely sending and receipt of notice of paragraph IV certification as described under 21 CFR 314.52(e) by each person required to receive notice. We note that the 45-day period provided for in section 505(c)(3)(C) of the FD&C Act would apply.

REDACTED

Sincerely,

{See appended electronic signature page}

Maarika Kimbrell
Director
Office of New Drug Policy
Office of New Drugs
Center for Drug Evaluation and Research

REDACTED

[60] See 21 CFR 314.50(i)(6)(ii).

Appendix A

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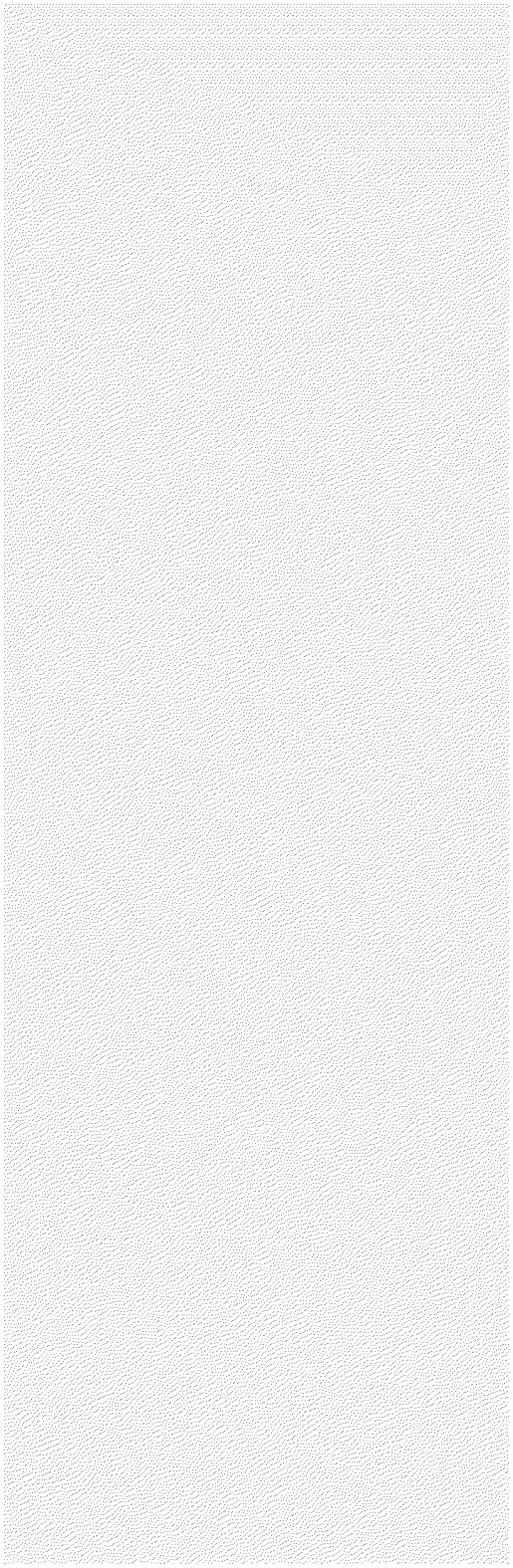
Avadel CNS Pharmaceuticals, LLC
Chesterfield, MO



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/s/

MAARIKA N KIMBRELL
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EXHIBIT L

US008731963B1

(12) **United States Patent**
Reardan et al.

(10) **Patent No.: US 8,731,963 B1**
(45) **Date of Patent: *May 20, 2014**

(54) **SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD**

(75) Inventors: **Dayton T. Reardan**, Shorewood, MN (US); **Patti A. Engel**, Eagan, MN (US); **Bob Gagne**, St. Paul, MN (US)

(73) Assignee: **Jazz Pharmaceuticals, Inc.**, Palo Alto, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/592,202**

(22) Filed: **Aug. 22, 2012**

Related U.S. Application Data

(63) Continuation of application No. 13/013,680, filed on Jan. 25, 2011, now abandoned, which is a continuation of application No. 12/704,097, filed on Feb. 11, 2010, now Pat. No. 7,895,059, which is a continuation of application No. 10/322,348, filed on Dec. 17, 2002, now Pat. No. 7,668,730.

(51) **Int. Cl.**
G06Q 10/00 (2012.01)

(52) **U.S. Cl.**
USPC **705/2**; 705/3; 707/803

(58) **Field of Classification Search**
USPC 707/803; 705/2, 3
See application file for complete search history.

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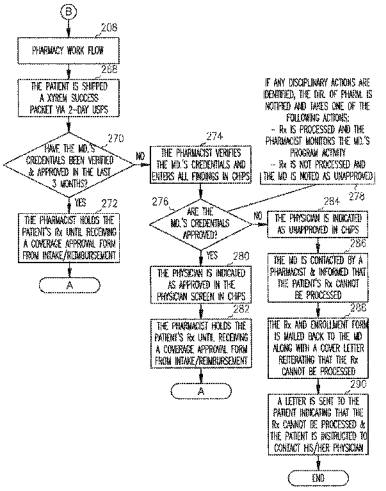
Primary Examiner — Lena Najarian
(74) *Attorney, Agent, or Firm* — Schwegman Lundberg & Woessner, P.A.

(57) **ABSTRACT**

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in the database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database, and optionally whether any actions are taken against the physician. Multiple controls beyond those for normal drugs are imposed on the distribution depending on the sensitivity of the drug.

28 Claims, 16 Drawing Sheets



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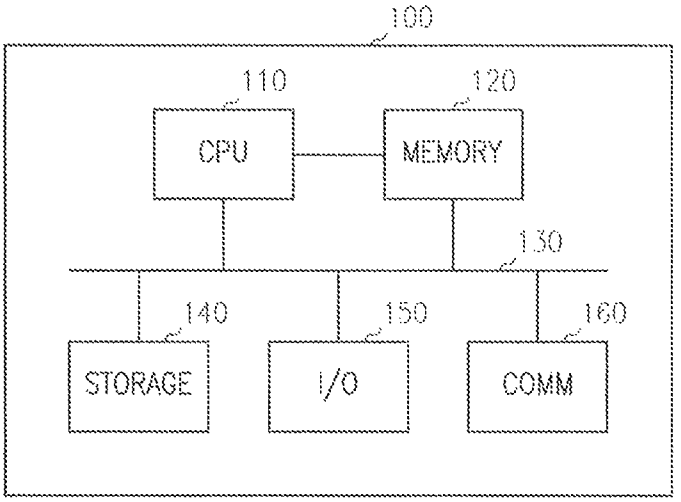
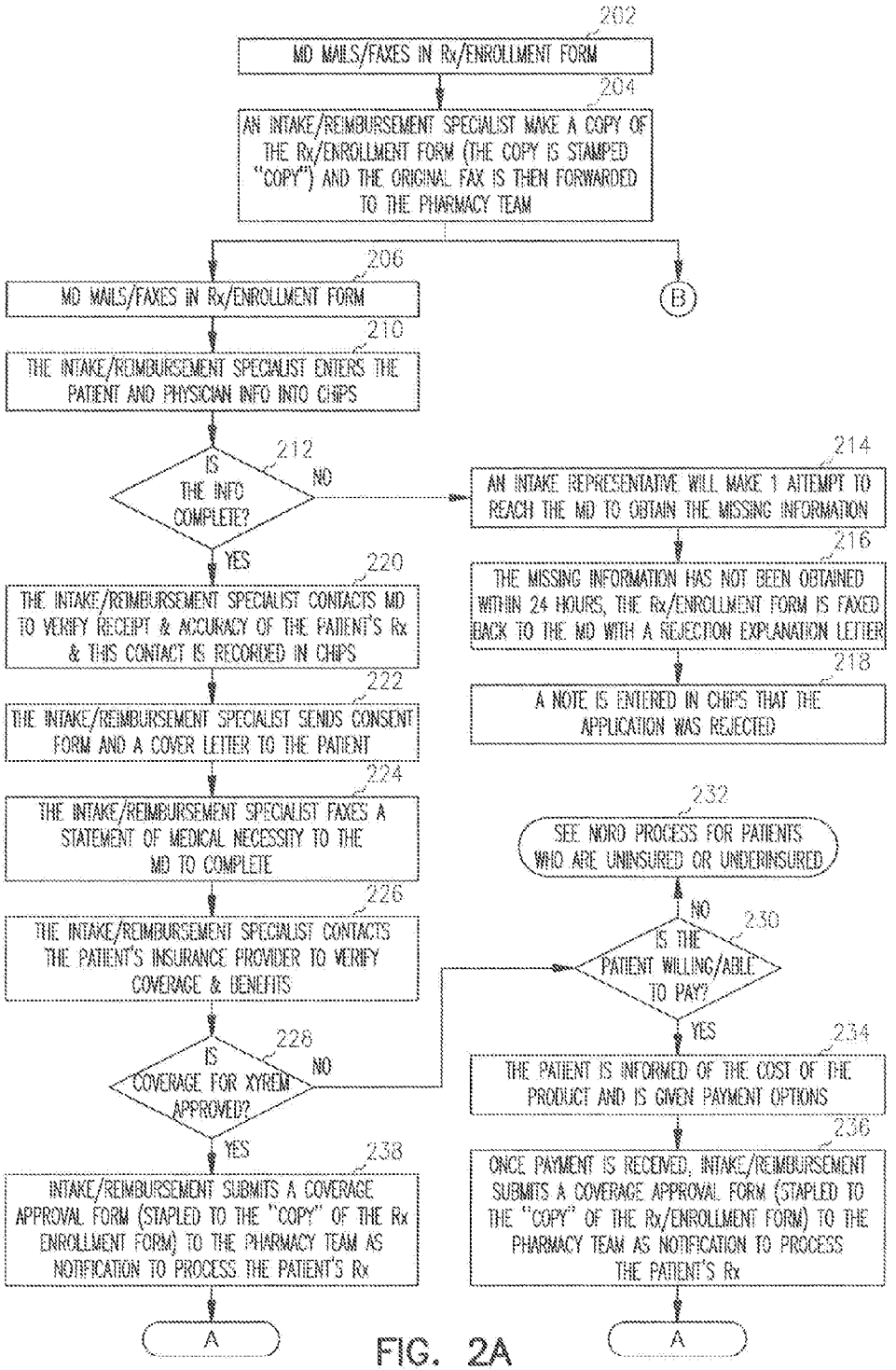


FIG. 1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204
AN INTAKE/REIMBURSEMENT SPECIALIST MAKE A COPY OF THE Rx/ENROLLMENT FORM (THE COPY IS STAMPED "COPY") AND THE ORIGINAL FAX IS THEN FORWARDED TO THE PHARMACY TEAM
206
MD MAILS/FAXES IN Rx/ENROLLMENT FORM
B
210
THE INTAKE/REIMBURSEMENT SPECIALIST ENTERS THE PATIENT AND PHYSICIAN INFO INTO CHIPS
212
IS THE INFO COMPLETE?
NO
YES
214
AN INTAKE REPRESENTATIVE WILL MAKE 1 ATTEMPT TO REACH THE MD TO OBTAIN THE MISSING INFORMATION
216
THE MISSING INFORMATION HAS NOT BEEN OBTAINED WITHIN 24 HOURS, THE Rx/ENROLLMENT FORM IS FAXED BACK TO THE MD WITH A REJECTION EXPLANATION LETTER
218
A NOTE IS ENTERED IN CHIPS THAT THE APPLICATION WAS REJECTED
220
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS MD TO VERIFY RECEIPT & ACCURACY OF THE PATIENT'S Rx & THIS CONTACT IS RECORDED IN CHIPS
222
THE INTAKE/REIMBURSEMENT SPECIALIST SENDS CONSENT FORM AND A COVER LETTER TO THE PATIENT
224
THE INTAKE/REIMBURSEMENT SPECIALIST FAXES A STATEMENT OF MEDICAL NECESSITY TO THE MD TO COMPLETE
226
THE INTAKE/REIMBURSEMENT SPECIALIST CONTACTS THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE & BENEFITS
228
IS COVERAGE FOR XYREM APPROVED?
NO
YES
232
SEE NORD PROCESS FOR PATIENTS WHO ARE UNINSURED OR UNDERINSURED
NO
230
IS THE PATIENT WILLING/ABLE TO PAY?
YES
234
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
236
ONCE PAYMENT IS RECEIVED, INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx/ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
238
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM (STAPLED TO THE "COPY" OF THE Rx ENROLLMENT FORM) TO THE PHARMACY TEAM AS NOTIFICATION TO PROCESS THE PATIENT'S Rx
A
A

FIG. 2A

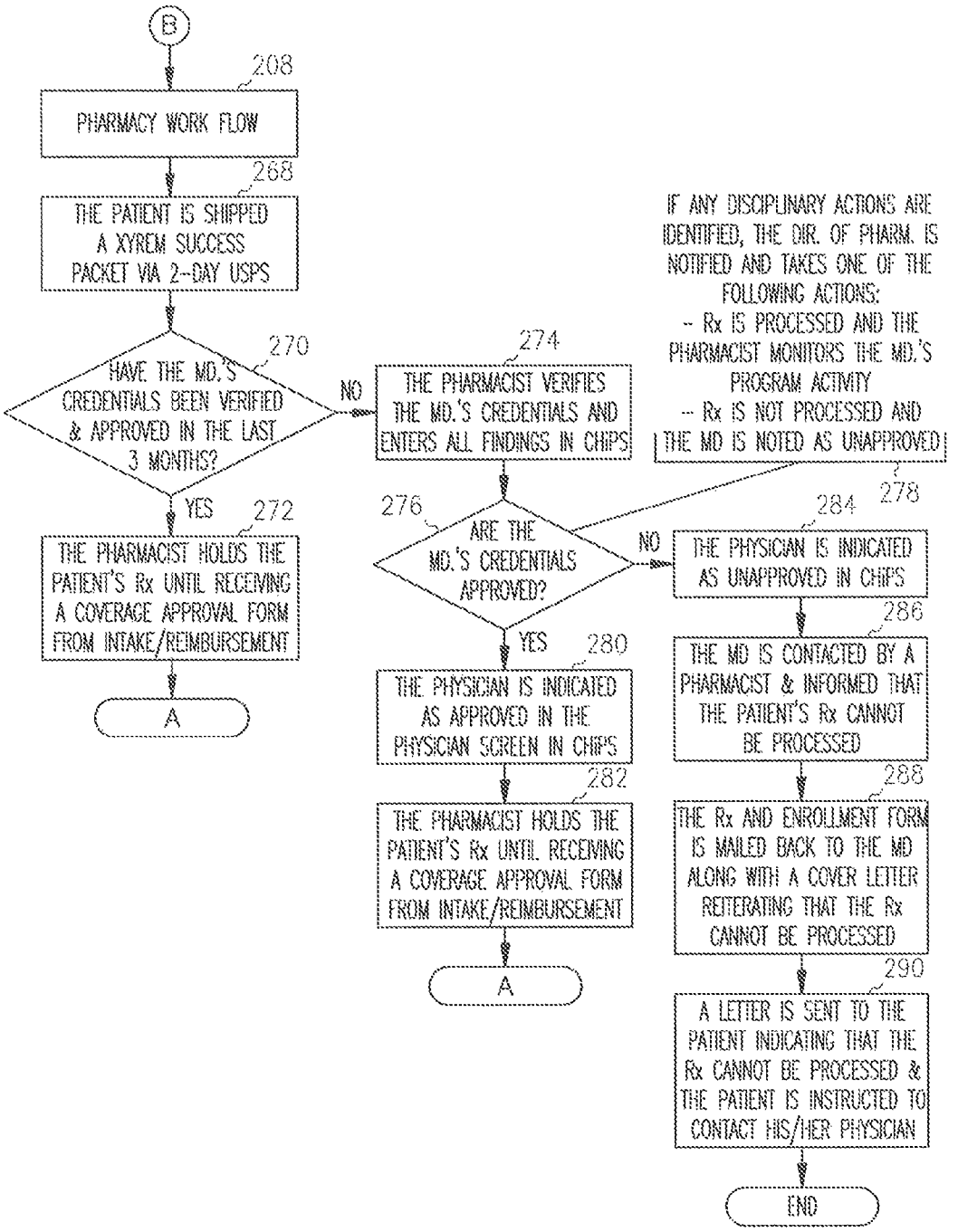
B
208
PHARMACY WORK FLOW
268
THE PATIENT IS SHIPPED A XYREM SUCCESS PACKET VIA 2-DAY USPS
270
HAVE THE MD.'S CREDENTIALS BEEN VERIFIED & APPROVED IN THE LAST 3 MONTHS?
NO
YES
272
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
274
THE PHARMACIST VERIFIES THE MD.'S CREDENTIALS AND ENTERS ALL FINDINGS IN CHIPS
276
ARE THE MD.'S CREDENTIALS APPROVED?
NO
YES
280
THE PHYSICIAN IS INDICATED AS APPROVED IN THE PHYSICIAN SCREEN IN CHIPS
282
THE PHARMACIST HOLDS THE PATIENT'S Rx UNTIL RECEIVING A COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT
A
IF ANY DISCIPLINARY ACTIONS ARE IDENTIFIED, THE DIR. OF PHARM. IS NOTIFIED AND TAKES ONE OF THE FOLLOWING ACTIONS:
- Rx IS PROCESSED AND THE PHARMACIST MONITORS THE MD.'S PROGRAM ACTIVITY
- Rx IS NOT PROCESSED AND THE MD IS NOTED AS UNAPPROVED
278
284
THE PHYSICIAN IS INDICATED AS UNAPPROVED IN CHIPS
286
THE MD IS CONTACTED BY A PHARMACIST & INFORMED THAT THE PATIENT'S Rx CANNOT BE PROCESSED
288
THE Rx AND ENROLLMENT FORM IS MAILED BACK TO THE MD ALONG WITH A COVER LETTER REITERATING THAT THE Rx CANNOT BE PROCESSED
290
A LETTER IS SENT TO THE PATIENT INDICATING THAT THE Rx CANNOT BE PROCESSED & THE PATIENT IS INSTRUCTED TO CONTACT HIS/HER PHYSICIAN
END

FIG. 2B

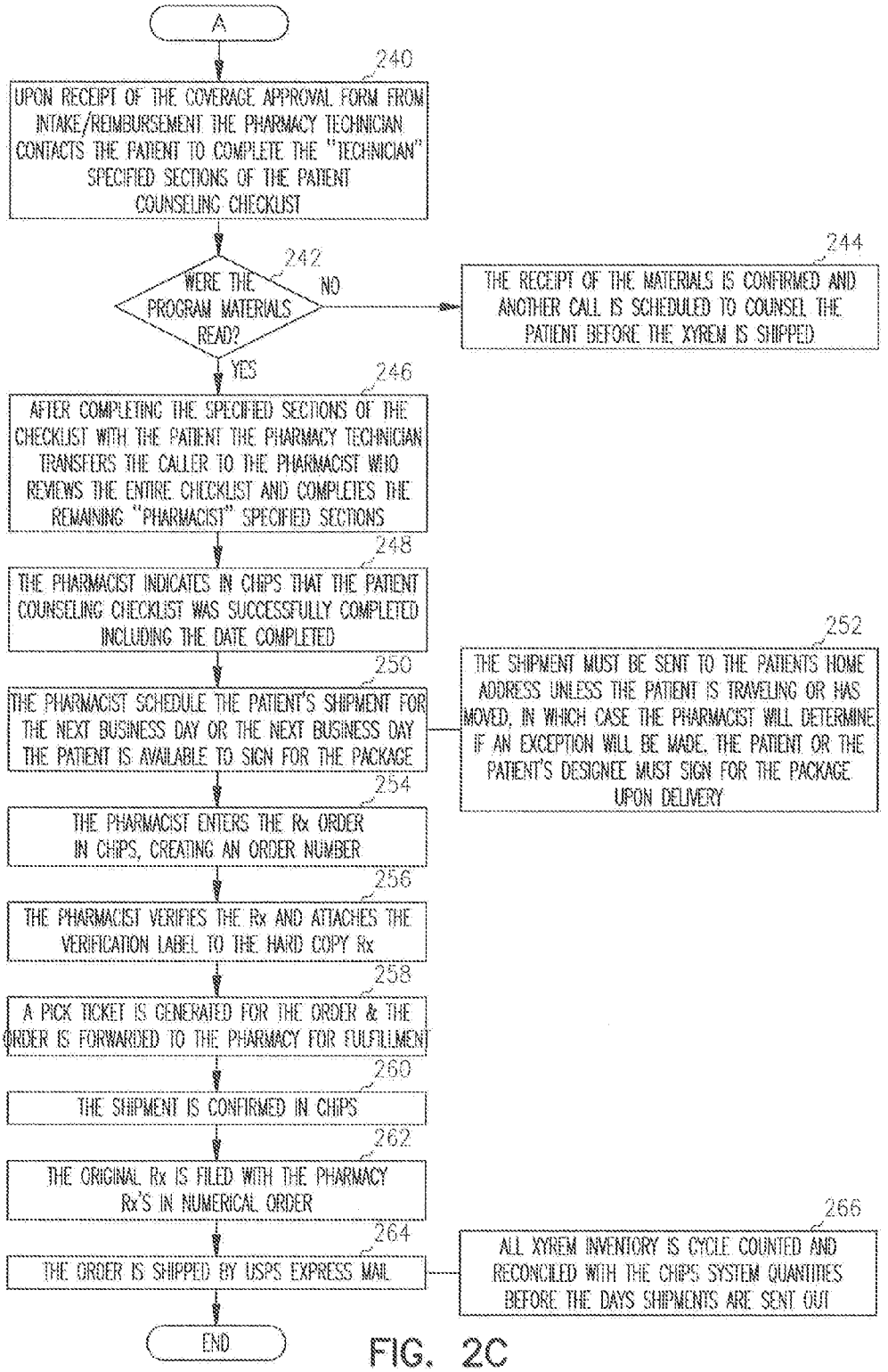
A
240
UPON RECEIPT OF THE COVERAGE APPROVAL FORM FROM INTAKE/REIMBURSEMENT THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE "TECHNICIAN" SPECIFIED SECTIONS OF THE PATIENT COUNSELING CHECKLIST
242
WERE THE PROGRAM MATERIALS READ?
NO
244
THE RECEIPT OF THE MATERIALS IS CONFIRMED AND ANOTHER CALL IS SCHEDULED TO COUNSEL THE PATIENT BEFORE THE XYREM IS SHIPPED
YES
246
AFTER COMPLETING THE SPECIFIED SECTIONS OF THE CHECKLIST WITH THE PATIENT THE PHARMACY TECHNICIAN TRANSFERS THE CALLER TO THE PHARMACIST WHO REVIEWS THE ENTIRE CHECKLIST AND COMPLETES THE REMAINING "PHARMACIST" SPECIFIED SECTIONS
248
THE PHARMACIST INDICATES IN CHIPS THAT THE PATIENT COUNSELING CHECKLIST WAS SUCCESSFULLY COMPLETED INCLUDING THE DATE COMPLETED
252
THE SHIPMENT MUST BE SENT TO THE PATIENTS HOME ADDRESS UNLESS THE PATIENT IS TRAVELING OR HAS MOVED, IN WHICH CASE THE PHARMACIST WILL DETERMINE IF AN EXCEPTION WILL BE MADE. THE PATIENT OR THE PATIENT'S DESIGNEE MUST SIGN FOR THE PACKAGE UPON DELIVERY
250
THE PHARMACIST SCHEDULE THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
254
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
256
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
258
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
260
THE SHIPMENT IS CONFIRMED IN CHIPS
262
THE ORIGINAL Rx IS FILED WITH THE PHARMACY Rx'S IN NUMERICAL ORDER
266
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
264
THE ORDER IS SHIPPED BY USPS EXPRESS MAIL
END

FIG. 2C

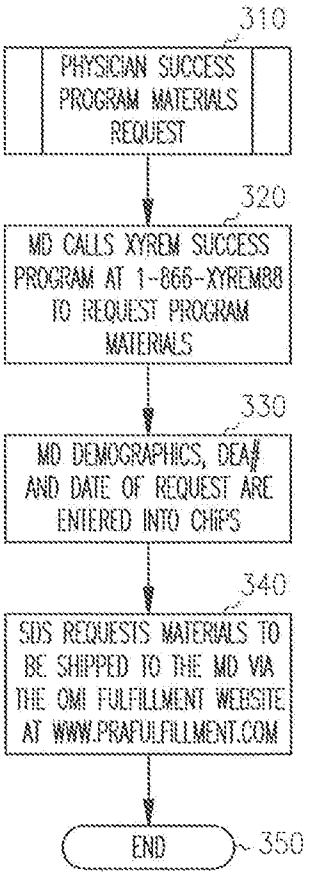
310
PHYSICIAN SUCCESS PROGRAM MATERIALS REQUEST
320
MD CALLS XYREM SUCCESS PROGRAM AT 1-866-XYREM88 TO REQUEST PROGRAM MATERIALS
330
MD DEMOGRAPHICS, DEA# AND DATE OF REQUEST ARE ENTERED INTO CHPS
340
SDS REQUESTS MATERIALS TO BE SHIPPED TO THE MD VIA THE OMI FULFILLMENT WEBSITE AT WWW.PRAFULFILLMENT.COM
END
350

FIG. 3

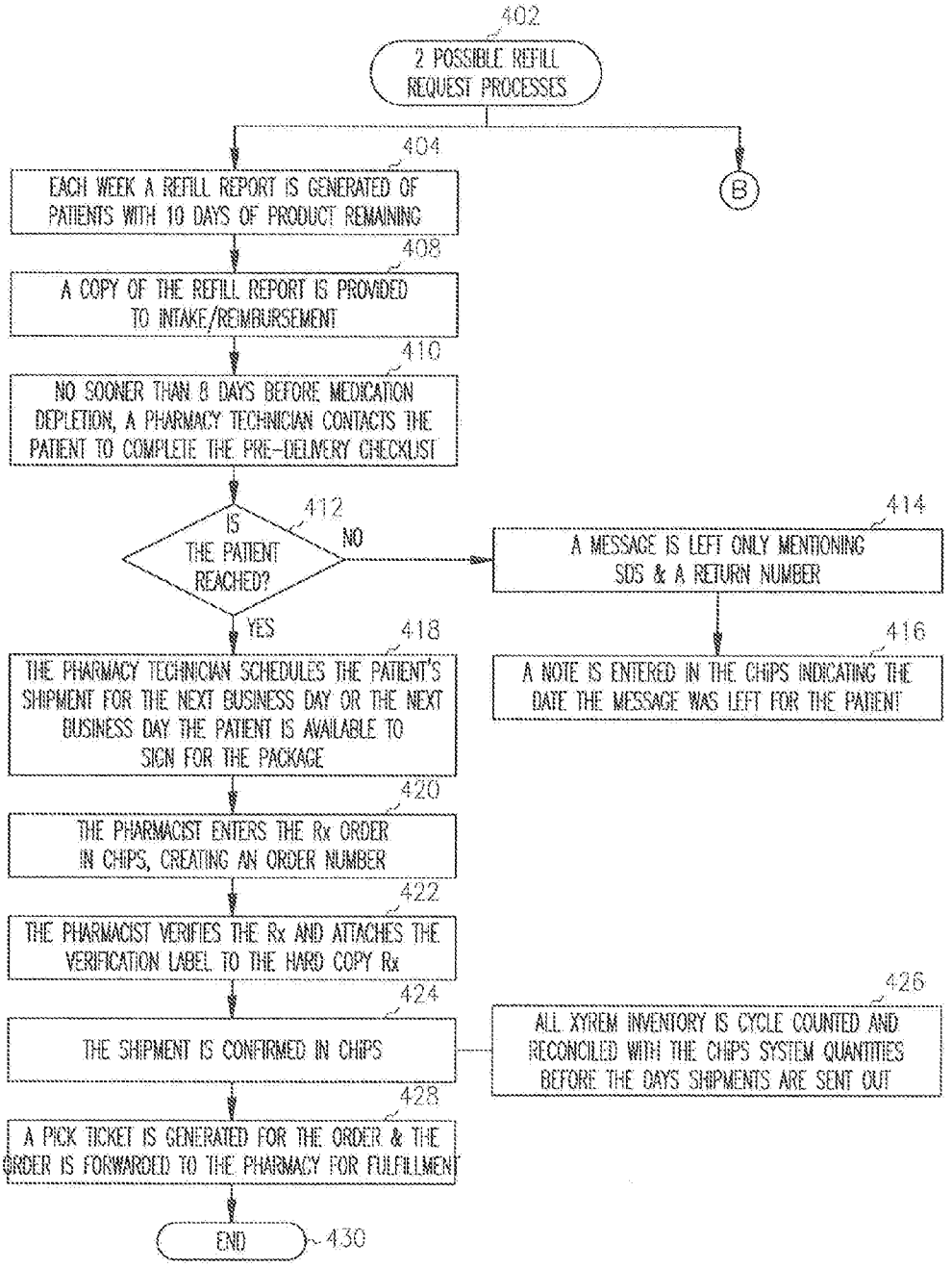
402
2 POSSIBLE REFILL REQUEST PROCESSES
404
EACH WEEK A REFILL REPORT IS GENERATED OF PATIENTS WITH 10 DAYS OF PRODUCT REMAINING
B
408
A COPY OF THE REFILL REPORT IS PROVIDED TO INTAKE/REIMBURSEMENT
410
NO SOONER THAN 8 DAYS BEFORE MEDICATION DEPLETION, A PHARMACY TECHNICIAN CONTACTS THE PATIENT TO COMPLETE THE PRE-DELIVERY CHECKLIST
412
IS THE PATIENT REACHED?
NO
414
A MESSAGE IS LEFT ONLY MENTIONING SOS & A RETURN NUMBER
YES
418
THE PHARMACY TECHNICIAN SCHEDULES THE PATIENT'S SHIPMENT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
416
A NOTE IS ENTERED IN THE CHIPS INDICATING THE DATE THE MESSAGE WAS LEFT FOR THE PATIENT
420
THE PHARMACIST ENTERS THE Rx ORDER IN CHIPS, CREATING AN ORDER NUMBER
422
THE PHARMACIST VERIFIES THE Rx AND ATTACHES THE VERIFICATION LABEL TO THE HARD COPY Rx
424
THE SHIPMENT IS CONFIRMED IN CHIPS
426
ALL XYREM INVENTORY IS CYCLE COUNTED AND RECONCILED WITH THE CHIPS SYSTEM QUANTITIES BEFORE THE DAYS SHIPMENTS ARE SENT OUT
428
A PICK TICKET IS GENERATED FOR THE ORDER & THE ORDER IS FORWARDED TO THE PHARMACY FOR FULFILLMENT
END
430

FIG. 4A

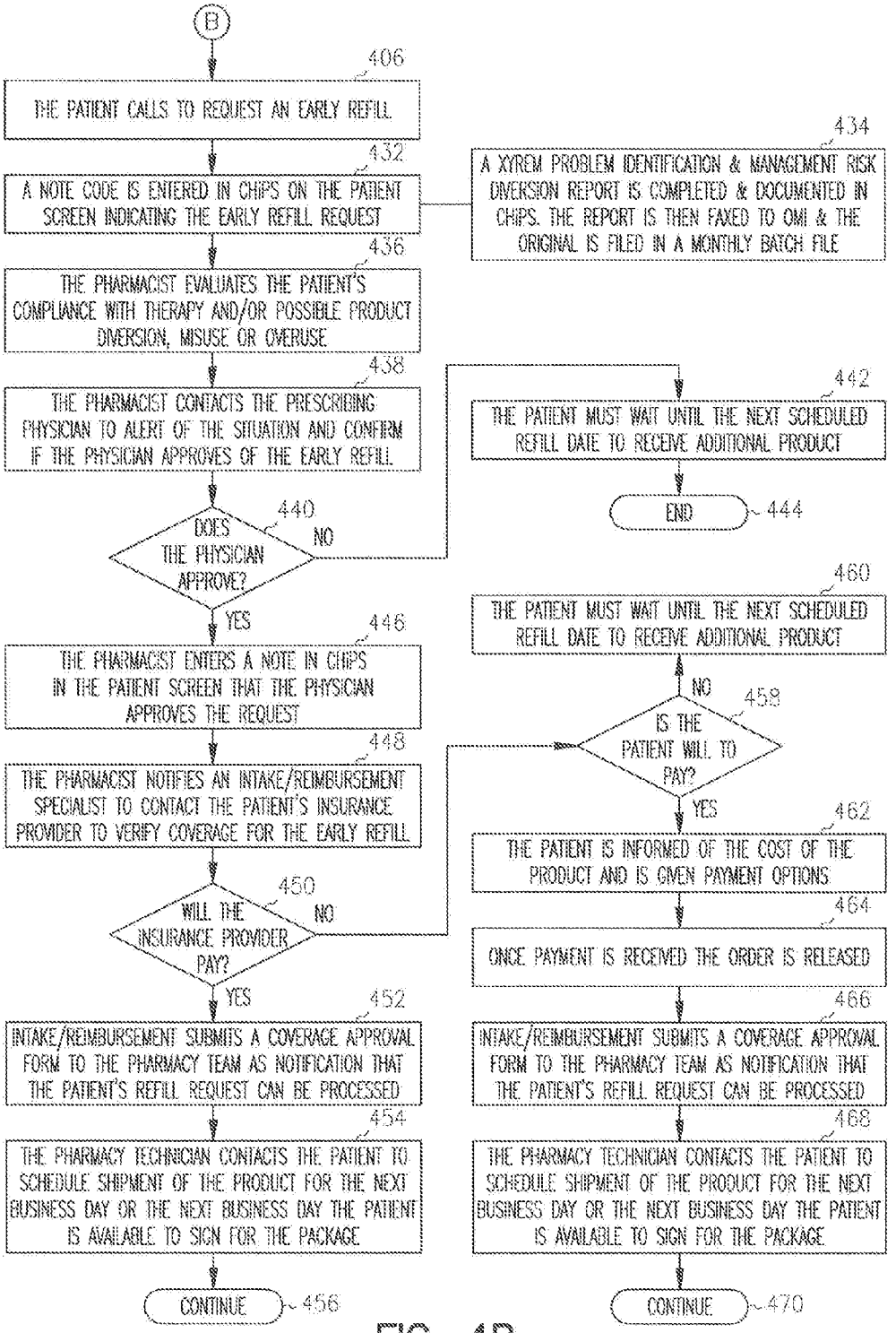
B
406
THE PATIENT CALLS TO REQUEST AN EARLY REFILL
432
A NOTE CODE IS ENTERED IN CHIPS ON THE PATIENT SCREEN INDICATING THE EARLY REFILL REQUEST
434
A XYROM PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORT IS COMPLETED & DOCUMENTED IN CHIPS. THE REPORT IS THEN FAXED TO OMI & THE ORIGINAL IS FILED IN A MONTHLY BATCH FILE
436
THE PHARMACIST EVALUATES THE PATIENT'S COMPLIANCE WITH THERAPY AND/OR POSSIBLE PRODUCT DIVERSION, MISUSE OR OVERUSE
438
THE PHARMACIST CONTACTS THE PRESCRIBING PHYSICIAN TO ALERT OF THE SITUATION AND CONFIRM IF THE PHYSICIAN APPROVES OF THE EARLY REFILL
440
DOES THE PHYSICIAN APPROVE?
NO
YES
442
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
END
444
446
THE PHARMACIST ENTERS A NOTE IN CHIPS IN THE PATIENT SCREEN THAT THE PHYSICIAN APPROVES THE REQUEST
448
THE PHARMACIST NOTIFIES AN INTAKE/REIMBURSEMENT SPECIALIST TO CONTACT THE PATIENT'S INSURANCE PROVIDER TO VERIFY COVERAGE FOR THE EARLY REFILL
450
WILL THE INSURANCE PROVIDER PAY?
NO
YES
452
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
454
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
456
460
THE PATIENT MUST WAIT UNTIL THE NEXT SCHEDULED REFILL DATE TO RECEIVE ADDITIONAL PRODUCT
NO
458
IS THE PATIENT WILL TO PAY?
YES
462
THE PATIENT IS INFORMED OF THE COST OF THE PRODUCT AND IS GIVEN PAYMENT OPTIONS
464
ONCE PAYMENT IS RECEIVED THE ORDER IS RELEASED
466
INTAKE/REIMBURSEMENT SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT'S REFILL REQUEST CAN BE PROCESSED
468
THE PHARMACY TECHNICIAN CONTACTS THE PATIENT TO SCHEDULE SHIPMENT OF THE PRODUCT FOR THE NEXT BUSINESS DAY OR THE NEXT BUSINESS DAY THE PATIENT IS AVAILABLE TO SIGN FOR THE PACKAGE
CONTINUE
470

FIG. 4B

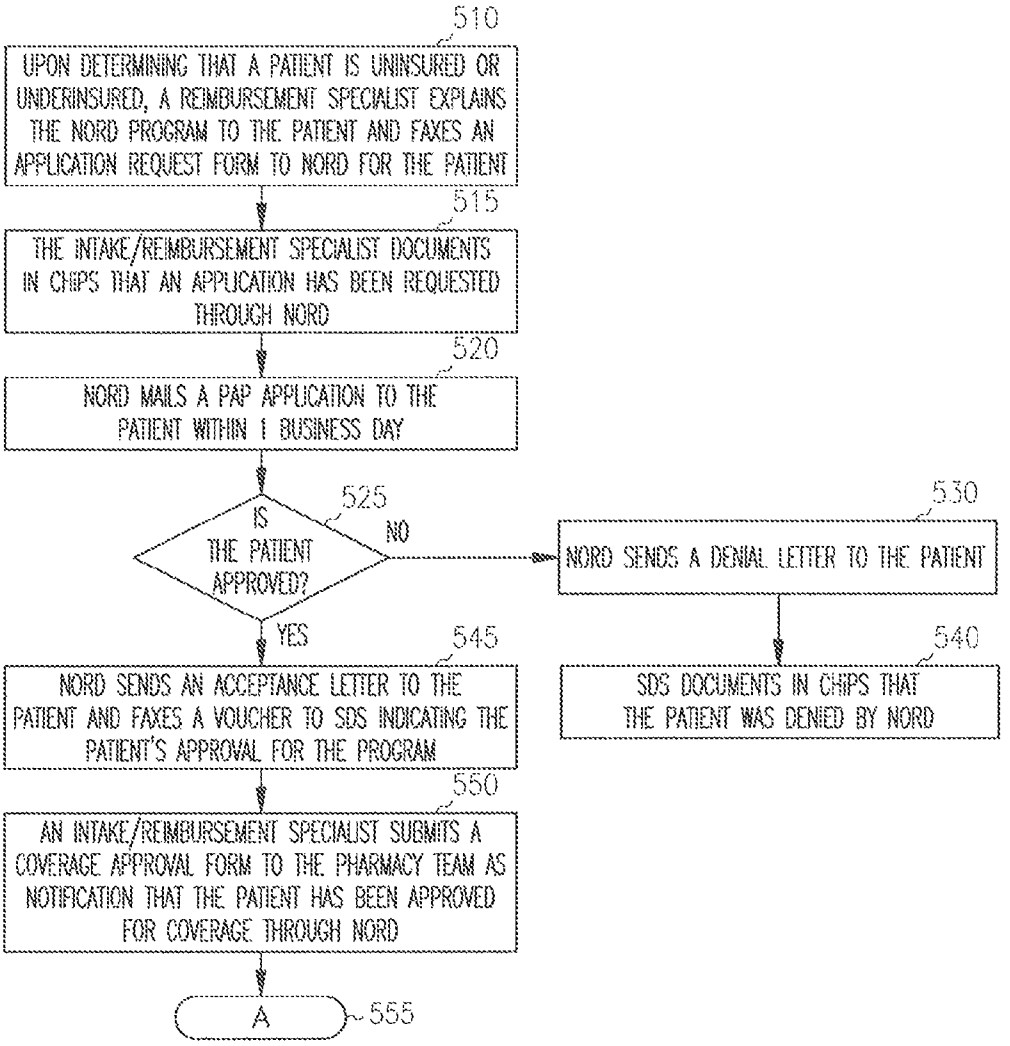
510
UPON DETERMINING THAT A PATIENT IS UNINSURED OR UNDERINSURED, A REIMBURSEMENT SPECIALIST EXPLAINS THE NORD PROGRAM TO THE PATIENT AND FAXES AN APPLICATION REQUEST FORM TO NORD FOR THE PATIENT
515
THE INTAKE/REIMBURSEMENT SPECIALIST DOCUMENTS IN CHIPS THAT AN APPLICATION HAS BEEN REQUESTED THROUGH NORD
520
NORD MAILS A PAP APPLICATION TO THE PATIENT WITHIN 1 BUSINESS DAY
525
IS THE PATIENT APPROVED?
NO
530
NORD SENDS A DENIAL LETTER TO THE PATIENT
YES
545
NORD SENDS AN ACCEPTANCE LETTER TO THE PATIENT AND FAXES A VOUCHER TO SDS INDICATING THE PATIENT'S APPROVAL FOR THE PROGRAM
540
SDS DOCUMENTS IN CHIPS THAT THE PATIENT WAS DENIED BY NORD
550
AN INTAKE/REIMBURSEMENT SPECIALIST SUBMITS A COVERAGE APPROVAL FORM TO THE PHARMACY TEAM AS NOTIFICATION THAT THE PATIENT HAS BEEN APPROVED FOR COVERAGE THROUGH NORD
A
555

FIG. 5

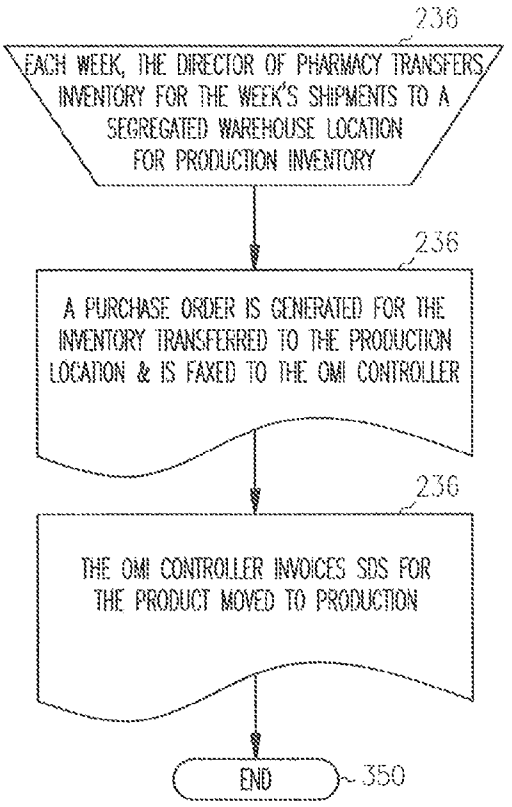

FIG. 6

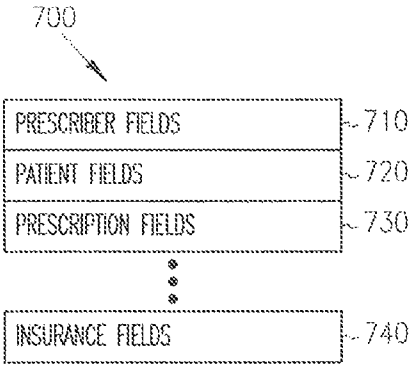

FIG. 7

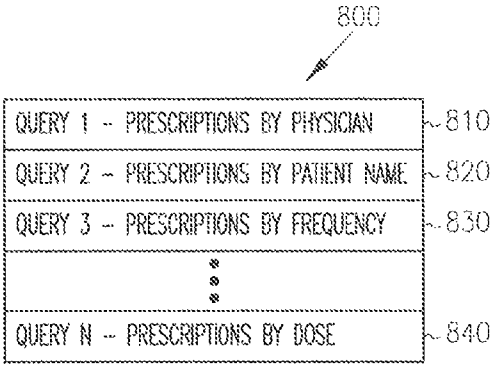

FIG. 8

900

PRESCRIPTION AND ENROLLMENT FORM

PRESCRIBER INFORMATION

PRESCRIBER'S NAME: ..... OFFICE CONTACT: .....
STREET ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
PHONE: ..... FAX: .....
LICENSE NUMBER: ..... DEA NUMBER: .....
MD SPECIALTY: .....

PRESCRIPTION FORM

PATIENT NAME: ..... SS#: ..... DOB: ..... SEX M / F
ADDRESS: .....
CITY: ..... STATE: ..... ZIP: .....
Rx: XYREM ORAL SOLUTION (500 mg/mL) 180 ML BOTTLE QUANTITY: ..... MONTHS SUPPLY
SIG: TAKE ..... GMS P.O. DILUTED IN 60 mL WATER AT H.S. AND THEN AGAIN 2 1/2 TO 4 HOURS LATER
REFILLS (CIRCLE ONE): 0 1 2 (MAXIMUM OF 3 MONTH SUPPLY)
..... DATE: ...../...../.....
PRESCRIBER'S SIGNATURE

PHYSICIAN DECLARATION–PLEASE CHECK EACH BOX | TO BE COMPLETED AT INITIAL PRESCRIPTION ONLY

☐ I HAVE READ THE MATERIALS IN THE XYREM PHYSICIAN SUCCESS PROGRAM
☐ I VERIFY THAT THE PATIENT HAS BEEN EDUCATED WITH RESPECT TO XYREM PREPARATION, DOSING AND SCHEDULING.
☐ I UNDERSTAND THAT XYREM IS APPROVED FOR THE TREATMENT OF CATAPLEXY IN PATIENTS WITH NARCOLEPSY, AND THAT SAFETY OR EFFICACY HAS NOT BEEN ESTABLISHED FOR ANY OTHER INDICATION.
☐ I UNDERSTAND THAT THE SAFETY OF DOSES GREATER THAN 9gm/DAY HAS NOT BEEN ESTABLISHED

PATIENT INFORMATION

BEST TIME TO CONTACT PATIENT: ☐ DAY ☐ NIGHT
DAY #: ..... EVENING #: .....
INSURANCE COMPANY NAME: ..... PHONE #: .....
INSURED'S NAME: ..... RELATIONSHIP TO PATIENT: .....
IDENTIFICATION NUMBER: ..... POLICY/GROUP NUMBER: .....
PRESCRIPTION CARD: ☐ NO ☐ YES IF YES, CARRIER: ..... POLICY #: ..... GROUP: .....

PLEASE ATTACH COPIES OF PATIENT'S INSURANCE CARDS

FAX COMPLETED FORM TO XYREM SUCCESS PROGRAM (TOLL-FREE) 1-866-470-1744
FOR INFORMATION, CALL THE XYREM TEAM (TOLL FREE) AT 1-866-XYREM88 (1-866-997-3688)

FIG. 9


1000
PATIENT ASSISTANCE APPLICATION REQUEST FORM
DATE:
TO: PATIENT ASSISTANCE ORGANIZATION
FROM: SDS
FAX #: 203-798-2291
PLEASE SEND A XYREM PATIENT ASSISTANCE PROGRAM APPLICATION TO:
PATIENT NAME
ADDRESS
TELEPHONE: ( )
PATIENT DOSAGE: (GRAMS) TWICE NIGHTLY FOR A TOTAL DOSAGE OF (GRAMS)
BOTTLES (THREE MONTHS SUPPLY)
BACKGROUND INFORMATION:

FIG. 10

SENSITIVE DRUG PATIENT ASSISTANCE PROGRAM 1100

VOUCHER REQUEST FOR MEDICATION

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREEM 180ml bll	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

NORD COPY

****

(DETACH HERE)

PATIENT INFORMATION
<FIRST NAME><LAST NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890
DOB: 01/01/1900
SSN: 123-45-6789
DRUG ALLOTMENT: 100%
LRD: 03/01/2001

PHYSICIAN INFORMATION
<PHYSICIAN NAME>
<ADDRESS 1>
<ADDRESS 2>
<CITY, STATE ZIP CODE>

PHONE: <123-456-7890

CASE CODE: ********

FIRST SHIPMENT THIS YEAR

DRUG	QUANTITY
XYREM 180ml bll	1

VALIDATION DATE: 03/01/2001
EXPIRATION DATE: 05/31/2001
ISSUE DATE: 03/15/2001

APPROVED _____

PHARMACY USE

FIG. 11

SENSITIVE DRUG PHYSICIAN'S CERTIFICATE
OF MEDICAL NEED

PATIENT INFORMATION

DATE: .....

NAME: .....
LAST FIRST M

DATE OF BIRTH: .....

DRUG BEING PRESCRIBED: XYREM

DIAGNOSIS/CONDITION FOR WHICH DRUG IS BEING PRESCRIBED: .....

ICD-9: .....

PHYSICIAN INFORMATION

PHYSICIAN'S NAME (PLEASE PRINT): .....

PHYSICIAN'S SIGNATURE: ..... DATE: .....

PLEASE FAX BACK TO SENSITIVE DRUG SUCCESS PROGRAM: (1-800-TOLL FREE NUMBER)

FIG. 12

ACTIVITY REPORTS

	REPORT FREQUENCY		
	WEEKLY	MONTHLY	QUARTERLY
SALES			
Rx BY ZIP (NEW AND TOTAL)	X	X	X
Rx BY PHYSICIAN BY ZIP	X	X	
$ BY ZIP	X	X	X
REGULATORY			
# OF PHYSICIAN REGISTRIES		X	
# OF DENIED PHYSICIAN REGISTRIES AND REASON		X	
# OF COMPLETED PATIENT REGISTRIES		X	
# OF PROBLEM IDENTIFICATION & MANAGEMENT RISK DIVERSION REPORTS COMPLETED	X		
# OF CYCLE COUNTS PERFORMED & ACCURACY OF EACH		X	
QUALITY ASSURANCE			
# OF PRODUCT DEFECTS/COMPLAINTS REPORTED, TYPE AND LOT #		X	
CALL CENTER			
# OF CALLS RECEIVED		X	
# OF CALLS INITIATED		X	
# OF CALLS ANSWERED IN 30 SECONDS, ETC.		X	
PERCENTAGE OF CALLS ANSWERED IN 30 SECONDS		X	
# OF ABANDONED CALLS		X	
% OF ABANDONED CALLS		X	
AVERAGE CALL LENGTH		X	
PHARMACY			
# OF FAXED Rx/ENROLLMENT FORMS		X	
# OF MAILED Rx/ENROLLEMENT FORMS		X	
# OF Rxs SHIPPED WITH 1, 2, 3, 4 ETC. DAYS (FROM THE TIME INITIAL RECEIPT TO SHIPMENT OF Rx)		X	
# OF PATIENT SUCCESS PACKETS SHIPPED		X	

FIG. 13A

ACTIVITY REPORTS

PHARMACY		X	
# OF PHYSICIAN SUCCESS PACKETS SHIPPED		X	
# OF COMPLETED SHIPMENTS		X	
# OF INCOMPLETE SHIPMENTS AND REASON		X	
# OF SHIPPING ERRORS		X	
# OF PAP SHIPMENTS		X	
# OF PAP APPLICATIONS		X	
# OF PAP APPROVALS		X	
# OF CANCELED ORDERS		X	
# OF USPS ERRORS		X	
INVENTORY		X	
# OF RETURNED PRODUCTS AND REASON		X	
# OF OUTDATED BOTTLES OF PRODUCT		X	
INVENTORY COUNTS OF CONSIGNMENT & PRODUCTION INVENTORY		X	
# OF UNITS RECEIVED		X	
LOTS RECEIVED		X	
REIMBURSEMENT		X	
# OF PENDED AND WHY		X	
# OF APPROVALS		X	
# OF DENIALS		X	
# OF REJECTIONS		X	
PAYOR TYPES		X	

FIG. 13B

ACTIVITY REPORTS

PATIENT CARE			
# OF ADVERSE EVENTS REPORTED AND TYPE		X	
# OF ADVERSE EVENTS SENT TO OMI		X	
# OF DOSING PROBLEMS AND TYPE		X	
# OF NONCOMPLIANCE EPISODES AND REASON		X	
# OF PATIENT COUNSELED AND REASON		X	
# OF PATIENTS DISCONTINUED AND REASON		X	
PATIENT CARE		X	
# OF PATIENTS REFERRED TO PHYSICIAN AND REASON		X	
# OF ACTIVE PATIENTS		X	
# OF NEW PATIENTS		X	
# OF RESTART PATIENTS		X	
# OF DISCONTINUED PATIENTS AND REASON		X	
DRUG INFORMATION		X	
# OF DRUG INFORMATION REQUESTS AND TYPE		X	
# OF CALLS TRIAGED TO OMI		X	

FIG. 13C

SENSITIVE DRUG DISTRIBUTION SYSTEM AND METHOD

RELATED APPLICATION

This application a Continuation of U.S. application Ser. No. 13/013,680, filed on Jan. 25, 2011, which is a Continuation of U.S. application Ser. No. 12/704,097, filed on Feb. 11, 2010 and issued on Feb. 22, 2011 as U.S. Pat. No. 7,895,059, which is a Continuation of U.S. application Ser. No. 10/322,348, filed on Dec. 17, 2002 and issued on Feb. 23, 2010 as U.S. Pat. No. 7,668,730, which applications are incorporated by reference herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to distribution of drugs, and in particular to the distribution of sensitive drugs.

BACKGROUND OF THE INVENTION

Sensitive drugs are controlled to minimize risk and ensure that they are not abused, or cause adverse reactions. Such sensitive drugs are approved for specific uses by the Food and Drug Administration, and must be prescribed by a licensed physician in order to be purchased by consumers. Some drugs, such as cocaine and other common street drugs are the object of abuse and illegal schemes to distribute for profit. Some schemes include Dr. shopping, diversion, and pharmacy thefts. A locked cabinet or safe is a requirement for distribution of some drugs.

Certain agents, such as gamma hydroxy buterate (GHB) are also abused, yet also are effective for therapeutic purposes such as treatment of daytime cataplexy in patients with narcolepsy. Some patients however, will obtain prescriptions from multiple doctors, and have them filled at different pharmacies. Still further, an unscrupulous physician may actually write multiple prescriptions for a patient, or multiple patients, who use cash to pay for the drugs. These patients will then sell the drug to dealers or others for profit.

There is a need for a distribution system and method that directly addresses these abuses. There is a further need for such a system and method that provides education and limits the potential for such abuse.

SUMMARY OF THE INVENTION

A drug distribution system and method utilizes a central pharmacy and database to track all prescriptions for a sensitive drug. Information is kept in a central database regarding all physicians allowed to prescribe the sensitive drug, and all patients receiving the drug. Abuses are identified by monitoring data in the database for prescription patterns by physicians and prescriptions obtained by patients. Further verification is made that the physician is eligible to prescribe the drug by consulting a separate database for a valid DEA license, and optionally state medical boards to determine whether any corrective or approved disciplinary actions relating to controlled substances have been brought against the physician. Multiple controls beyond those for traditional drugs are imposed on the distribution depending on the sensitivity of the drug.

Education is provided to both physician and patient. Prior to shipping the drug for the first time, the patient is contacted to ensure that product and abuse related educational materials have been received and/or read. The patient may provide the name of a designee to the central pharmacy who is authorized

to accept shipment of the drug. Receipt of the initial drug shipment is confirmed by contacting the patient. Either a phone call or other communication to the patient within a set time after delivery may be made to ensure receipt. Further, a courier service's tracking system is used to confirm delivery in further embodiments. If a shipment is lost, an investigation is launched to find it.

In one embodiment, the drug may be shipped by the central pharmacy to another pharmacy for patient pick-up. The second pharmacy's ability to protect against diversion before shipping the drug must be confirmed. This ability may be checked through NTIS and State Boards of Pharmacy.

Prescription refills are permitted in the number specified in the original prescription. In addition, if a prescription refill is requested by the patient prior to the anticipated due date, such refills will be questioned. A lost, stolen, destroyed or spilled prescription/supply is documented and replaced to the extent necessary to honor the prescription, and will also cause a review or full investigation.

The exclusive central database contains all relevant data related to distribution of the drug and process of distributing it, including patient, physician and prescription information. Several queries and reports are run against the database to provide information which might reveal potential abuse of the sensitive drug, such as early refills.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a block diagram of a computer system for use in implementing the system and method of the present invention.

FIGS. **2**A, **2**B and **2**C are a flowchart describing a method for sensitive drug distribution at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **3** is a flowchart of a physician success program at least partially implemented on a computer system such as that shown in FIG. **1**.

FIGS. **4**A and **4**B are a flowchart describing a method for handling refill requests at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **5** is a flowchart of a process for requesting special reimbursement when a patient is uninsured or underinsured at least partially utilizing a computer system as that shown in FIG. **1**.

FIG. **6** is a flowchart of a process for inventory control at least partially utilizing a computer system such as that shown in FIG. **1**.

FIG. **7** is a block diagram of database fields.

FIG. **8** is a block diagram showing a list of queries against the database fields.

FIG. **9** is a copy of one example prescription and enrollment form.

FIG. **10** is a copy of one example of a NORD application request form for patient financial assistance.

FIG. **11** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**.

FIG. **12** is a copy of certificate of medical need.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**.

DETAILED DESCRIPTION OF THE INVENTION

In the following description, reference is made to the accompanying drawings that form a part hereof, and in which is shown by way of illustration specific embodiments in

which the invention may be practiced. These embodiments are described in sufficient detail to enable those skilled in the art to practice the invention, and it is to be understood that other embodiments may be utilized and that structural, logical and electrical changes may be made without departing from the scope of the present invention. The following description is, therefore, not to be taken in a limited sense, and the scope of the present invention is defined by the appended claims.

The functions or algorithms described herein are implemented in software or a combination of software and human implemented procedures in one embodiment. The software comprises computer executable instructions stored on computer readable media such as memory or other type of storage devices. The term "computer readable media" is also used to represent carrier waves on which the software is transmitted. Further, such functions correspond to modules, which are software, hardware, firmware of any combination thereof. Multiple functions are performed in one or more modules as desired, and the embodiments described are merely examples. The software is executed on a digital signal processor, ASIC, microprocessor, or other type of processor operating on a computer system, such as a personal computer, server or other computer system.

A sensitive drug is one which can be abused, or has addiction properties or other properties that render the drug sensitive. One example of such a drug is sodium oxybate, also known as gamma hydroxy butyrate (GHB $C_4H_7NaO_3$) which is useful for treatment of cataplexy in patients with narcolepsy. GHB is marketed under the trademark of Xyrem® (sodium oxybate oral solution), which trademark can be used interchangeably with GHB herein. Sensitive drugs also include narcotics or other drugs which require controls on their distribution and use to monitor behaviors to prevent abuse and adverse side effects.

In one embodiment, Xyrem® is subject to a restricted distribution program. One aspect of the program is to educate physicians and patients about the risks and benefits of Xyrem, including support via ongoing contact with patients and a toll free helpline. Initial prescriptions are filled only after a prescriber and patient have received and read the educational materials. Further, patient and prescribing physician registries are maintained and monitored to ensure proper distribution.

In a further embodiment, bulk sodium oxybate is manufactured at a single site, as is the finished drug product. Following manufacture of the drug product, it is stored at a facility compliant with FDA Schedule III regulations, where a consignment inventory is maintained. The inventory is owned by a company, and is managed by a central pharmacy, which maintains the consignment inventory. Xyrem® is distributed and dispensed through a primary and exclusive central pharmacy, and is not stocked in retail pharmacy outlets. It is distributed by overnight carriers, or by US mail in one embodiment to potentially invoke mail fraud laws if attempts of abuse occur.

FIG. **1** is a simplified block diagram of a computer system **100**, such as a personal computer for implementing at least a portion of the methods described herein. A central processing unit (CPU) **110** executes computer programs stored on a memory **120**. Memory **120** in one embodiment comprises one or more levels of cache as desired to speed execution of the program and access to data on which the programs operate. The CPU is directly coupled to memory **120** in one embodiment. Both CPU **110** and memory **120** are coupled to a bus **130**. A storage **140**, I/O **150** and communications **160** are also coupled to the bus **130**. Storage **140** is usually a long term storage device, such as a disk drive, tape drive, DVD, CD or other type of storage device. In one embodiment, storage **140** is used to house a database for use with the present invention. I/O **150** comprises keyboards, sound devices, displays and other mechanisms by which a user interacts with the computer system **100**. Communications **160** comprises a network, phone connection, local area network, wide area network or other mechanism for communicating with external devices. Such external devices comprise servers, other peer computers and other devices. In one embodiment, such external device comprises a database server that is used in place of the database on storage **140**. Other computer system architectures capable of executing software and interacting with a database and users may also be used. Appropriate security measures such as encryption are used to ensure confidentiality. Further, data integrity and backup measures are also used to prevent data loss.

FIGS. **2**A, **2**B and **2**C represent an initial prescription order entry process for a sensitive drug, such as Xyrem. At **202**, a medical doctor (MD) sends a Rx/enrollment form via mail, fax, email or other means to an intake/reimbursement specialist at **204**, who makes a copy of the RX/enrollment form that is stamped "copy". The original fax is forwarded to a pharmacy team. The enrollment form contains prescriber information, prescription information, checkboxes for the prescriber indicating they have read materials, educated the patient, understand the use in treatment, and understand certain safety information, and also contains patient information.

The prescriber information contains standard contact information as well as license number, DEA number and physician specialty. Patient and prescription information includes name, social security number, date of birth, gender, contact information, drug identification, patient's appropriate dosage, and number of refills allowed, along with a line for the prescriber's signature. Patient insurance information is also provided.

There are two workflows involved at the pharmacy team, intake reimbursement **206** and pharmacy workflow **208**, which may proceed in parallel or serially. The intake work flow **206** starts with an intake reimbursement specialist entering the patient and physician information into an application/database referred to as CHIPS, which is used to maintain a record of a client home infusion program (CHIP) for Xyrem®. A check is made to ensure the information is complete at **212**. If not, at **214**, an intake representative attempts to reach the MD or prescriber to obtain the missing information. If the missing information has not been obtained within a predetermined period of time, such as 24 hours at **216**, the Rx/Enrollment form is sent back to the MD with a rejection explanation. A note is entered in CHIPS that the application was rejected.

If the information is complete at **212**, the MD is contacted at **220** to verify receipt and accuracy of the patient's Rx. This contact is recorded in CHIPS. The intake and reimbursement specialist then sends a consent form and a cover letter to the patient at **224**. The insurance provider is contacted at **226** to verify coverage and benefits. At **228**, a determination is made regarding coverage for the drug. If it is not available, it is determined at **230** whether the patient is willing and able to pay. If not, a process is performed for handling patients who are uninsured or underinsured. In one embodiment, the process is referred to as a NORD process.

If the patient is willing and able to pay at **230**, the patient is informed of the cost of the product and is given payment options at **234**. At **236**, once payment is received, the intake reimbursement specialist submits a coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. If coverage is approved

at **228**, the intake reimbursement specialist also submits the coverage approval form with the enrollment form to the pharmacy team as notification to process the patient's prescription. Processing of the prescription is described below.

Upon receipt and initial processing of the prescription enrollment form and sending an original to the pharmacy work flow block **208**, the patient is shipped a Xyrem® success packet via mail. In one embodiment, the Xyrem® success packet contains educational material for a patient that advises of the proper use, care and handling of the drug and consequences of diversion at **268**. The medical doctor's credentials are checked to determine if the physician has a current DEA license to prescribe controlled substances and if he or she has had any actions related to misuse/misprescribing of controlled drugs against him or her, within a predetermined time, such as three months at **270**. If they have, a pharmacist holds the prescription until receiving a coverage approval form from the intake reimbursement specialist at **272**.

If the credentials have not been recently checked, the pharmacist verifies the credentials and enters all findings in the database at **274**. If the credentials are approved at **276**, the physician is indicated as approved in a physician screen populated by information from the database at **280**. The prescription is then held pending coverage approval at **282**.

If any disciplinary actions are identified, as referenced at block **278**, management of the pharmacy is notified and either approves processing of the prescription with continued monitoring of the physician, or processing of the prescription is not performed, and the physician is noted in the database as unapproved at **284**. The enrollment form is then mailed back to the physician with a cover letter reiterating that the prescription cannot be processed at **288**. The patient is also sent a letter at **290** indicating that the prescription cannot be processed and the patient is instructed to contact their physician.

Actual filling of the approved prescription begins with receipt of the coverage approval form as indicated at **240**. The patient is contacted by the pharmacy, such as by a technician to complete a technician section of a patient counseling checklist. If a pharmacist verifies that the program materials were not read at **242**, the receipt of the material is confirmed at **244** and another call is scheduled to counsel the patient before the drug is shipped.

If the program materials, were read at **242**, the checklist is completed at **246** and the technician transfers the patient to the pharmacist who reviews the entire checklist and completes remaining pharmacist specified sections. At **248**, the pharmacists indicates in the database that the patient counseling and checklist was successfully completed, indicating the date completed.

At **250**, the pharmacist schedules the patient's shipment for the next business day or the next business day that the patient or designee is able to sign for the package. Further, as indicated at **252**, the shipment must be sent to the patient's home address unless the patient is traveling or has moved. In that event, the pharmacist may determine that an exception may be made. The patient or the patient's designee who is at least 18 years old, must sign for the package upon delivery.

At **254**, the pharmacist enters the prescription order in the database, creating an order number. The pharmacist then verifies at **256** the prescription and attaches a verification label to the hard copy prescription. At **258**, a pick ticket is generated for the order and the order is forwarded to the pharmacy for fulfillment. The shipment is confirmed in the database at **260**, and the order is shipped by USPS Express Mail. Use of the US mail invokes certain criminal penalties for unauthorized diversion. Optionally, other mail services may be used. Potential changes in the law may also bring criminal penalties into play. Following shipment, the patient is called by the central pharmacy to confirm that the prescription was received.

As noted at **266**, for the sensitive drug, Xyrem, all inventory is cycle counted and reconciled with the database system quantities before shipments for the day are sent. This provides a very precise control of the inventory.

A physician success program materials request process begins at **310** in FIG. **3**. At **320**, the MD calls to the central pharmacy to request program materials. A special phone number is provided. MD demographics, DEA number, and data or request are entered into the database at **330**. At **340**, a request is made to ship the materials to the MD via a fulfillment website, or other mechanism. The request process ends at **350**.

A refill request process begins at **302** in FIGS. **4**A and **4**B. There are two different paths for refills. A first path beginning at **404** involves generating a report from the central database of patients with a predetermined number of days or product remaining. A second path beginning at **406** is followed when a patient calls to request an early refill.

In the first path, a copy of the report is provided to an intake reimbursement specialist at **408**. No sooner than 8 days before the medication depletion, a pharmacy technician contacts the patient at **410** to complete the pre-delivery **30** checklist. At **412**, if the patient is not reached, a message is left mentioning the depletion, and a return number at **414**. A note is also entered into the database indicating the date the message was left at **416**.

If the patient is reached at **412**, the next shipment is scheduled at **418**, the prescription is entered into the database creating an order at **420**, the pharmacist verifies the prescription and attaches a verification label at **422** and the shipment is confirmed in the database at **424**. Note at **426** that the inventory is cycle counted and reconciled with the database quantities before the shipments for a day or other time period are sent. A pick ticket is generated for the order and the order is forwarded for fulfillment at **428**, with the first path ending at **430**.

The second path, beginning at **406** results in a note code being entered into the database on a patient screen indicating an early refill request at **432**. The pharmacist evaluates the patient's compliance with therapy or possible product diversion, misuse or over-use at **436**. In one embodiment, cash payers are also identified. The pharmacist then contacts the prescribing physician to alert them of the situation and confirm if the physician approves of the early refill at **438**. If the physician does not approve as indicated at **440**, the patient must wait until the next scheduled refill date to receive additional product as indicated at **442**, and the process ends at **444**.

If the physician approves at **440**, the pharmacist enters a note in the database on a patient screen that the physician approves the request at **446**. The pharmacist notifies an intake reimbursement specialist to contact the patient's insurance provider to verify coverage for the early refill at **448**. If the insurance provider will pay as determined at **450**, the specialist submits the coverage approval form as notification that the refill may be processed at **452**. At **454**, the pharmacy technician contacts the patient to schedule shipment of the product for the next business day, and the process of filling the order is continued at **456** by following the process beginning at **240**.

If the insurance provider will not pay at **450**, it is determined whether the patient is willing and/or able to pay at **458**. If not, the patient must wait until the next scheduled refill date to receive additional product at **460**. If it was determined at **458** that the patient was willing and able to pay, the patient is informed of the cost of the product and is given payment

options at **462**. Once payment is received as indicated at **464**, the specialist submits a coverage approval form to the pharmacy team as notification that the refill request can be processed at **466**. At **468**, the pharmacy technician contacts the patient to schedule shipment. The process of filling the order is continued at **470** by following the process beginning at **240**.

A process, referred to as a NORD process in one embodiment is used to determine whether donated, third party funds are available for paying for prescriptions where neither insurance will, nor the patient can pay. The process begins at **510** upon determining that a patient is uninsured or underinsured. A reimbursement specialist explains the NORD program to the patient and faxes an application request form to NORD for the patient. At **515**, the intake reimbursement specialist documents in the database that an application has been received through NORD. At **520**, NORD mails an application to the patient within one business day.

A determination is made at **525** by NORD whether the patient is approved. If not, at **530**, NORD sends a denial letter to the patient, and it is documented in the database at **540** that the patient was denied by NORD. If the patient is approved, NORD sends an acceptance letter to the patient and faxes a voucher to the central pharmacy (SDS in one embodiment) to indicate the approval at **545**. At **550**, an intake reimbursement specialist submits a coverage approval form to the pharmacy team as notification that the patient has been approved for coverage. The process of filling the order is continued at **555** by following the process beginning at **240**.

An inventory control process is illustrated in FIG. **6** beginning at **610**. Each week, a responsible person at the central pharmacy, such as the director of the pharmacy transfers inventory for the week's shipments to a segregated warehouse location for production inventory. At **620**, a purchase order is generated for the inventory transferred to the production location and is sent, such as by fax, to a controller, such as the controller of the company that obtained approval for distribution and use of the sensitive drug. At **630**, the controller invoices the central pharmacy for the product moved to production. The process ends at **640**.

The central database described above is a relational database running on the system of FIG. **1**, or a server based system having a similar architecture coupled to workstations via a network, as represented by communications **160**. The database is likely stored in storage **140**, and contains multiple fields of information as indicated at **700** in FIG. **7**. The organization and groupings of the fields are shown in one format for convenience. It is recognized that many different organizations or schemas may be utilized. In one embodiment, the groups of fields comprise prescriber fields **710**, patient fields **720**, prescription fields **730** and insurance fields **740**. For purposes of illustration, all the entries described with respect to the above processes are included in the fields. In further embodiments, no such groupings are made, and the data is organized in a different manner.

Several queries are illustrated at **800** in FIG. **8**. There may be many other queries as required by individual state reporting requirements. A first query at **810** is used to identify prescriptions written by physician. The queries may be written in structured query language, natural query languages or in any other manner compatible with the database. A second query **820** is used to pull information from the database related to prescriptions by patient name. A third query **830** is used to determine prescriptions by frequency, and a n^{th} query finds prescriptions by dose at **840**. Using query languages combined with the depth of data in the central database allows many other methods of investigating for potential abuse of the drugs. The central database ensures that all prescriptions, prescribers and patients are tracked and subject to such investigations. In further embodiments, the central database may be distributed among multiple computers provided a query operates over all data relating to such prescriptions, prescribers and patients for the drug.

An example of one prescription and enrollment form is shown at **900** in FIG. **9**. As previously indicated, several fields are included for prescriber information, prescription information and patient information.

FIG. **10** is a copy of one example NORD application request form **1000** used to request that an application be sent to a patient for financial assistance.

FIG. **11** is a copy of one example application **1100** for financial assistance as requested by form **1000**. The form requires both patient and physician information. Social security number information is also requested. The form provides information for approving the financial assistance and for tracking assistance provided.

FIG. **12** is a copy of one example voucher request for medication for use with the NORD application request form of FIG. **10**. In addition to patient and physician information, prescription information and diagnosis information is also provided.

FIGS. **13**A, **13**B and **13**C are descriptions of sample reports obtained by querying a central database having fields represented in FIG. **7**. The activities grouped by sales, regulatory, quality assurance, call center, pharmacy, inventory, reimbursement, patient care and drug information. Each report has an associated frequency or frequencies. The reports are obtained by running queries against the database, with the queries written in one of many query languages.

While the invention has been described with respect to a Schedule III drug, it is useful for other sensitive drugs that are DEA or Federally scheduled drugs in Schedule II-V, as well as still other sensitive drugs where multiple controls are desired for distribution and use.

The invention claimed is:

1. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor configured to:

process a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug; and

reconcile inventory of the prescription drug before the shipments for a day or other time period are sent by using

said database query to identify information in the prescription fields and patient fields;

wherein the data processor is configured to process a second database query that identifies that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

2. The system of claim **1**, wherein the data processor selectively blocks shipment of the prescription drug to the patient based upon said identifying by the database query.

3. The system of claim **1**, wherein the prescription drug is shipped to the narcoleptic patient if no potential misuse, abuse or diversion is found for the narcoleptic patient.

4. The system of claim **1**, wherein the single computer database is an exclusive database that receives data associated with all patients being prescribed the prescription drug that is associated with the company.

5. The system of claim **1**, wherein an exclusive central pharmacy controls the single computer database.

6. The system of claim **1** wherein the prescription drug comprises gamma hydroxyl butyrate (GHB).

7. The system of claim **1**, wherein the single computer database comprises a relational database.

8. The system of claim **1**, wherein the single computer database is distributed among multiple computers and the database query operates over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

9. The system of claim **1**, wherein the data processor is configured to initiate an inquiry to a prescriber when one or more prescription fields, patient fields, or prescriber fields are incomplete in the computer database.

10. The system of claim **1**, wherein the data processor is configured to process a third database query that identifies an expected date for a refill of the prescription drug.

11. The system of claim **10**, wherein the expected date is based on a prescription for the prescription drug and a date of a previous filling of the prescription.

12. The system of claim **11**, wherein the prescription identifies an amount of the prescription drug to be provided and a schedule for consumption of the prescription drug.

13. The system of claim **1**, wherein the database schema further contains and interrelates insurance fields, wherein the insurance fields, contained within the database schema, store information sufficient to identify an insurer to be contacted for payment for prescription drugs of an associated patient.

14. The system of claim **1**, wherein the single computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug; wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

15. The system of claim **14**, wherein one or more controls for distribution of the prescription drug are selected based on the identified pattern.

16. The system of claim **15**, wherein the one or more controls are submitted to an approval body for approval of distribution of the prescription drug.

17. The system of claim **1**, wherein additional controls for distribution are selected in a negotiation with an approval body to garner the approval of distribution.

18. The system of claim **17**, wherein the data processor is used to add further controls until approval is obtained.

19. The system of claim **18**, wherein the approval body is the Food and Drug Administration (FDA) or the Drug Enforcement Agency (DEA).

20. The system of claim **1**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

21. The system of claim **1**, wherein the single computer database comprises an exclusive computer database of the company that obtained approval for distribution of the prescription drug, wherein all prescriptions for the company's prescription drug are stored only in the exclusive computer database of the company, and wherein the company's prescription drug is sold or distributed by the company using only the exclusive computer database of the company.

22. The system of claim **1**, wherein the single computer database comprises a single computer database of the company that obtained approval for distribution of the prescription drug, wherein the prescription fields store all prescription requests, for all patients being prescribed the company's prescription drug, only in the single computer database of the company, from all physicians or other prescribers allowed to prescribe the company's prescription drug, such that all prescriptions for the company's prescription drug are processed using only the single computer database of the company.

23. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, comprising:

one or more computer memories for storing a single computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify a physician or other prescriber of the company's prescription drug and information to show that the physician or other prescriber is authorized to prescribe the company's prescription drug;

a data processor for processing a database query that operates over all data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said database query identifying information in the prescription fields and patient fields for reconciling inventory of the prescription drug before the shipments for a day or other time period are sent, wherein an inventory reconciliation is performed where current inventory is counted and reconciled with database quantities before shipments for a day or other time period are sent, and wherein the data processor is configured to selectively block shipment of the prescription drug based on the inventory reconciliation;

wherein the data processor is configured to process a second database query that identifies that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

24. A computer-implemented system for treatment of a narcoleptic patient with a prescription drug that has a potential for misuse, abuse or diversion, wherein the prescription drug is sold or distributed by a company that obtained approval for distribution of the prescription drug, comprising:

one or more computer memories for storing a central computer database of the company that obtained approval for distribution of the prescription drug, for receiving prescriptions from any and all patients being prescribed the company's prescription drug, said central computer database having a database schema that contains and interrelates prescription fields, patient fields, and prescriber fields;

said central computer database being distributed over multiple computers;

said prescription fields, contained within the database schema, storing prescriptions for the prescription drug with the potential for abuse, misuse or diversion;

said patient fields, contained within the database schema, storing information sufficient to identify the narcoleptic patient for whom the company's prescription drug is prescribed;

said prescriber fields, contained within the database schema, storing information sufficient to identify any and all physicians or other prescribers of the company's prescription drug and information to show that the physicians or other prescribers are authorized to prescribe the company's prescription drug;

one or more data processors for processing one or more database queries that operate over data related to the prescription fields, prescriber fields, and patient fields for the prescription drug;

said one or more database queries checking for abuse within the central computer database, wherein the filling of the prescriptions is authorized for the company's prescription drug only if there is no record of incidents that indicate abuse, misuse, or diversion by the narcoleptic patient and prescriber and if there is a record of such incidents, the central computer database indicates that such incidents have been investigated, and the central computer database indicates that such incidents do not involve abuse, misuse or diversion.

25. The system of claim **24**, wherein the one or more database queries are processed by the one or more data processors for identifying: that the narcoleptic patient is a cash payer and a physician that is interrelated with the narcoleptic patient through the schema of the single computer database;

said identifying that the narcoleptic patient is a cash payer by said second database query being an indicator of a potential misuse, abuse or diversion by the narcoleptic patient and being used to notify the physician that is interrelated with the narcoleptic patient through the schema of the single computer database.

26. The system of claim **24**, where the central computer database is distributed among multiple computers, and where the one or more database queries operate over all data relating to said prescription fields, prescriber fields, and patient fields for the prescription drug.

27. The system of claim **24**, wherein the central computer database is used to identify a current pattern or an anticipated pattern of abuse of the prescription drug;

wherein the current pattern or the anticipated pattern are identified using periodic reports generated from the single computer database.

28. The system of claim **24**, wherein current inventory is cycle counted and reconciled with database quantities before shipments for a day or other time period are sent.

* * * * *

EXHIBIT M

Evaluate Vantage

October 18, 2021

Avadel delay hands Jazz another narcolepsy boost

Amy Brown

A delay to the FDA's decision on Avadel's narcolepsy project, FT218, allows Jazz investors a second bout of schadenfreude in as many weeks. The once-a-night pill could become a big competitor to Jazz's twice-a-night Xyrem/Xyway franchise; the news follows the exit of another potential rival, Takeda's TAK-994, recently abandoned on safety concerns. When the FDA's verdict on FT218, which had a Pdufa date of October 15, might emerge is unclear. Avadel insists the regulator made no new information requests, saying only that action was unlikely in October. A short delay due to a lack of resources at the agency would be the best case scenario. However, the FDA could be mulling more serious issues, Stifel analysts mooted: firstly that Avadel might need to go down the generic filing route – Xyrem/Xyway and FT218 contain the same active ingredient – a scenario that would lead to a 30-month stay to approval. Or perhaps the agency is considering whether FT218 really deserves orphan drug exclusivity, which is largely based on its dosage advantage. A 15% drop in Avadel's stock this morning suggests investors are cautiously optimistic that the delay will be short. The outlook for the narcolepsy market, below, shows what is in play.

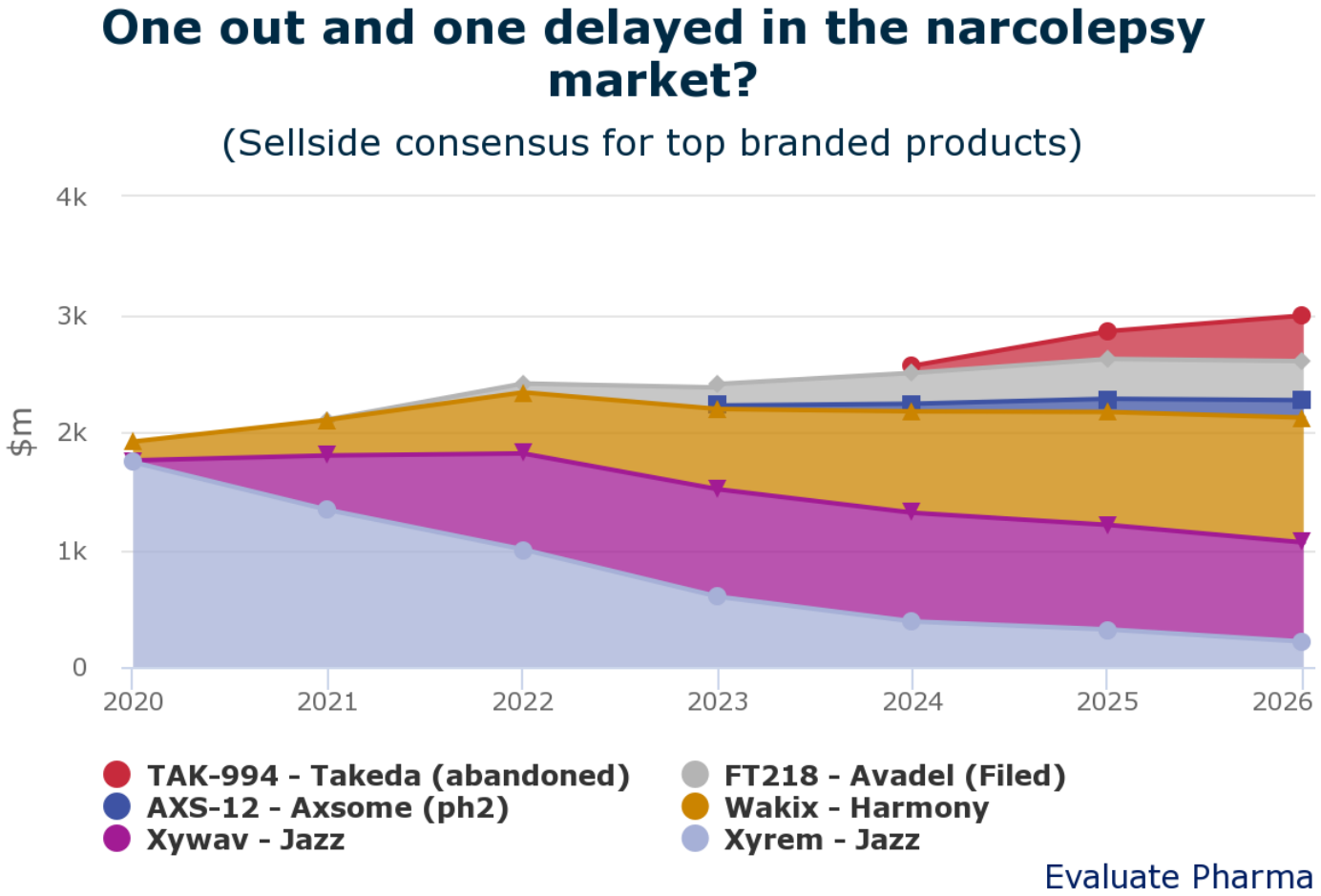

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EXHIBIT N

The FDA Is Expected to Approve New Narcolepsy Drug

Research Report

Biotechnology / Pharmaceuticals (/pub/htdocs/exclusive_articles.html?prod_type=20;utm_source=na_tags)

(7/5/22)

Avadel Pharmaceuticals Plc., the biopharma company behind this treatment, is currently undervalued and rated Outperform, noted an Oppenheimer report.

Avadel Pharmaceuticals Plc (AVDL:NASDAQ) (https://www.streetwisereports.com/pub/co/9789) is working to expedite final U.S. Food and Drug Administration (FDA) approval of FT218 ahead of June 2023, Oppenheimer's estimate of when it will happen, reported analyst Francois Brisebois in a July 1 research note. However, Avadel and Oppenheimer expect the FDA will grant tentative approval of the narcolepsy drug candidate in the interim.

"As we continue to anticipate tentative approval in the near term, we are reiterating our Outperform rating and $13 price target" on Avadel, Brisebois wrote, adding the drug developer is currently undervalued. Its share price now is around $2.87.

The FDA is currently reviewing Avadel's new drug application for FT218 to treat Ehlers Danlos syndrome and cataplexy in adults diagnosed with narcolepsy. The company "received and agreed to the expected final label" and is finalizing its risk evaluation and mitigation strategy (REMS), Brisebois wrote.

Oppenheimer expects final approval of FT218 to coincide with the REMS patent expiration of Jazz Pharmaceuticals' Xyrem (sodium oxybate), currently being used to treat narcolepsy symptoms.

However, Ireland-headquartered Avadel has filed a motion to delist the patent, for which a claim hearing is scheduled for Aug. 31, 2022. The outcome of this proceeding could favor Avadel, which "would represent upside to our base case," commented Brisebois.

Based on its interactions with the FDA, the biopharma expects the agency will give FT218 orphan drug exclusivity.

As for the market opportunity for FT218, it is "hard to overstate," Brisebois described. According to Avadel, the population for FT218 could be between 30,000 and 35,000 patients.

"Interestingly, Avadel highlighted that about 3,000 patients start oxybate annually with growth expectations of 25–50% with FT218," relayed Brisebois.

Given the delays in approval of FT218 (the PDUFA date was Oct. 15 of last year), Avadel started cutting operating costs, as expected, Brisebois wrote. The biotech anticipates having about $100 million ($100M) at the end of Q2/22. Two of its convertible notes mature next year, the $26.4M one in February and the $117.4M one in October.

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EXHIBIT O

Avadel gets tentative FDA nod for rival to Jazz narcolepsy drug

By **Nick Paul Taylor** · Jul 26, 2022 07:50am

Avadel Pharmaceuticals | Jazz Pharmaceuticals | Xyrem | extended-release

Lumryz poses a threat to Jazz's Xyrem, the twice-nightly incumbent in the narcolepsy market. (FDA)

Avadel Pharmaceuticals has taken a step toward challenging Jazz Pharmaceuticals for the narcolepsy market. The FDA granted tentative approval to the company's extended-release rival to Xyrem, leaving a patent as the last barrier between it and the market.

Today, narcolepsy patients who take sodium oxybate to treat excessive daytime sleepiness and sudden muscle weakness need to take two doses a night. The short half-life and immediate-release formulation means a second dose is needed around three hours after the first. Avadel wants to enable once-nightly dosing by bringing an extended-release sodium oxybate formulation to market.

The FDA gave tentative approval to the candidate, Lumryz, last week, indicating that Avadel had met all the quality, safety and efficacy standards needed to bring the drug to market in the U.S. Avadel aims to launch Lumryz by June 2023, but the timing of the final approval depends on a patent owned by Jazz.

Last month, Avadel filed a motion to delist the Jazz patent, which describes a sensitive drug distribution system and method, from the FDA's Orange Book. If the court requires Jazz to delist the patent, Avadel could win final approval before June 2023. Avadel is also preparing for a claim construction hearing that is set to take place at the end of next month.

RELATED

FDA missing more approval target dates as COVID slows inspections

Lumryz poses a threat to Jazz's Xyrem, the twice-nightly incumbent in the narcolepsy market. Based on its less burdensome dosing schedule, Avadel expects Lumryz to become the treatment of choice once it comes to market.

Jazz is fighting back in the courts, launching multiple legal actions last year and following up around the same time as the FDA granted tentative approval with a lawsuit that alleges the infringement of a patent.

Drug Delivery | Pharma | narcolepsy

EXHIBIT P

Avadel Pharmaceuticals Announces Tentative Approval of LUMRYZ™ (sodium oxybate) extended-release oral suspension

July 19, 2022

- Validates the safety profile and clinical efficacy of LUMRYZ

- Pursuing strategies to accelerate final approval

DUBLIN, Ireland, July 19, 2022 (GLOBE NEWSWIRE) -- Avadel Pharmaceuticals plc (Nasdaq: AVDL), a biopharmaceutical company focused on transforming medicines to transform lives, today announced that the U.S. Food and Drug Administration (FDA) has granted tentative approval to LUMRYZ, also known as FT218. Tentative approval indicates that LUMRYZ has met all required quality, safety, and efficacy standards necessary for approval in the U.S. Final approval is pending disposition of U.S. Patent No. 8,731,963 (the "REMS patent") which is listed in FDA's Orange Book. LUMRYZ is a once-at-bedtime investigational formulation of sodium oxybate for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adults with narcolepsy.

"We have reached a critical milestone, as tentative approval confirms the safety profile and clinical efficacy of LUMRYZ for adults with narcolepsy," said Greg Divis, Chief Executive Officer at Avadel Pharmaceuticals. "Tentative approval is an important regulatory step forward and indicates LUMRYZ could potentially be granted final approval in 11 months or less. We believe once-at-bedtime LUMRYZ offers the opportunity to positively transform the lives of oxybate eligible patients living with narcolepsy. Our extensive market research indicates Avadel is well-positioned to capture significant share of the oxybate eligible patient population which we estimate to be in excess of 30,000 patients. We are pursuing all options to accelerate final approval on or before June 2023 and prepare for commercial launch."

With tentative approval now secured, Avadel is continuing the following actions, including those that can potentially accelerate FDA's final approval decision and shorten the timeline between approval and launch of LUMRYZ:

- Filed a motion in the U.S. District Court for the District of Delaware on June 23, 2022, to delist the REMS patent from FDA's Orange Book. A court order requiring the patent holder to delist the REMS patent from the Orange Book could provide a pathway for a final approval of LUMRYZ prior to June 2023.
- Preparing for a claim construction hearing ("Markman hearing") scheduled for August 31, 2022, that the Court previously stated is needed in order to rule on the pending patent delisting motion.
- Continuing key activities in anticipation of final approval, including planning for the final preparation of the LUMRYZ REMS program and the continued manufacturing of commercial supply.

Based on extensive patient and physician research, Avadel estimates the total patient population could be greater than 30,000, and expects LUMRYZ, if approved, to be the treatment of choice for patients suffering from narcolepsy-related EDS or cataplexy. The current twice-nightly U.S. narcolepsy oxybate market is estimated at $1.8 billion comprised of approximately 16,000 patients. In addition, Avadel estimates that in the last three years, 10,000 – 15,000 patients have discontinued their twice-nightly oxybate use, many due to complications associated with middle of the night dosing. Furthermore, based on an analysis of U.S. claims data, the Company believes that each year approximately 3,000 patients initiate oxybate treatment for the first time and expects this to grow by 25-50% over time with the introduction of LUMRYZ. Based on the estimated total patient population, the potential market opportunity could be in excess of $3.0 billion annually.

About LUMRYZ
LUMRYZ is an investigational formulation of sodium oxybate leveraging our proprietary drug delivery technology and designed to be taken once at bedtime for the treatment of EDS or cataplexy in adults with narcolepsy.

In March 2020, Avadel completed the REST-ON trial, a randomized, double-blind, placebo-controlled, pivotal Phase 3 trial, to assess the efficacy and safety of LUMRYZ in adults with narcolepsy. Among the three co-primary endpoints, LUMRYZ demonstrated statistically significant and clinically meaningful results in EDS, the clinician's overall assessment of the patient's functioning, and reduction in cataplexy attacks for all three evaluated doses compared to placebo.

In January 2018, the FDA granted LUMRYZ Orphan Drug Designation for the treatment of narcolepsy based on the plausible hypothesis that LUMRYZ may be clinically superior to the twice-nightly formulation of sodium oxybate already approved by the FDA for those with narcolepsy due to the consequences of middle-of-the-night dosing of the approved product.

On July 18, 2022, the FDA tentatively approved the LUMRYZ NDA for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy. Final approval of LUMRYZ cannot be granted until the expiration or other disposition of U.S. Patent No. 8,731,963, which expires on June 17, 2023.

Avadel is currently evaluating the long-term safety and tolerability of LUMRYZ in the open-label RESTORE clinical study. For more information, visit: www.restore-narcolepsy-study.com.

About Avadel Pharmaceuticals plc
Avadel Pharmaceuticals plc (Nasdaq: AVDL) is a biopharmaceutical company focused on transforming medicines to transform lives. Our approach

includes applying innovative solutions to the development of medications that address the challenges patients face with current treatment options. Our current lead drug candidate, LUMRYZ, is an investigational formulation of sodium oxybate leveraging our proprietary drug delivery technology and designed to be taken once at bedtime for the treatment of excessive daytime sleepiness and cataplexy in adults with narcolepsy. For more information, please visit www.avadel.com.

Cautionary Disclosure Regarding Forward-Looking Statements
This press release includes "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. These forward-looking statements relate to our future expectations, beliefs, plans, strategies, objectives, results, conditions, financial performance, prospects, or other events. Such forward-looking statements include, but are not limited to, the timing and receipt of final approval from the FDA of the LUMRYZ NDA, the results of the Company's efforts to accelerate the FDA's final approval decision and to accelerate the timing between approval and launch, if approved. In some cases, forward-looking statements can be identified by the use of words such as "will," "may," "could," "believe," "expect," "look forward," "on track," "guidance," "anticipate," "estimate," "project," "next steps" and similar expressions, and the negatives thereof (if applicable).

Our forward-looking statements are based on estimates and assumptions that are made within the bounds of our knowledge of our business and operations and that we consider reasonable. However, our business and operations are subject to significant risks, and, as a result, there can be no assurance that actual results and the results of our business and operations will not differ materially from the results contemplated in such forward-looking statements. Factors that could cause actual results to differ from expectations in our forward-looking statements include the risks and uncertainties described in the "Risk Factors" section of Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2021, which we filed with the Securities and Exchange Commission on March 16, 2022, and subsequent SEC filings.

Forward-looking statements speak only as of the date they are made and are not guarantees of future performance. Accordingly, you should not place undue reliance on forward-looking statements. We do not undertake any obligation to publicly update or revise our forward-looking statements, except as required by law.

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EXHIBIT Q

Request for Fast Track Designation for Sodium Oxybate for Extended-Release Oral Suspension (FT218)

For the Treatment of Cataplexy and Excessive Daytime Sleepiness In Narcolepsy

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IND Number:	126321

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1. INTRODUCTION

Oxybate, also known as gamma-hydroxybutyric acid (GHB) was discovered in 1960. GHB is a metabolite of gamma-aminobutyric acid (GABA), which is synthesized by neurons in the brain and functions as a neurotransmitter. GHB is a central nervous system (CNS) depressant and produces dose-dependent sedation and anesthesia in laboratory animals (WHO 2012). GHB is used for the treatment of narcolepsy and alcohol withdrawal and has recently been proposed as an experimental therapeutic for depression (Liechti 2016). GHB has also received increasing attention due to its use as a recreational substance (Brailsford 2016).

The sodium salt of GHB, sodium oxybate, has been described as a therapeutic agent with high medical value (Fuller 2004, U.S. Xyrem® Multicenter Study Group 2004). In Europe and the U.S., sodium oxybate is currently indicated for the treatment of cataplexy and excessive daytime sleepiness (EDS) in patients with narcolepsy at doses up to 9.0 g/night (Xyrem® Summary of Product Characteristics (SmPC) 2015, Xyrem® U.S. Package Insert 2018). A recent post hoc analysis confirmed that sodium oxybate treatment results in improved sleep continuity and nocturnal sleep quality in patients with narcolepsy (Roth et al. 2017). Moreover, sodium oxybate treatment is associated with improvements in resistance to sleep and sustained attention in narcoleptic patients (van Schie 2016).

In the U.S., the Food and Drug Administration (FDA) approved, in 2002, Xyrem® (sodium oxybate) oral solution as an orphan drug for the treatment of cataplexy in adult patients with narcolepsy (Xyrem® U.S. Package Insert 2018). In 2005, this approval was extended to the treatment of EDS in adults with narcolepsy, and, in 2018, it was further extended to the pediatric population. In Europe, sodium oxybate was granted Orphan Drug Designation in February 2003. The European Commission issued a decision in 2005 for its marketing authorization for the treatment of cataplexy in adult patients with narcolepsy that was extended in 2007 to the treatment of EDS in adults with narcolepsy (Xyrem® SmPC 2015). The orphan designation was withdrawn from the Community Register of designated orphan medicinal products in January 2010 on request of the sponsor.

Sodium oxybate has also been approved in different countries for various purposes, such as general anesthesia and treatment of alcohol withdrawal and addiction. Potential additional benefits of sodium oxybate include the treatment of symptoms of idiopathic hypersomnia (Leu-Semenescu 2016).

Xyrem® is administered in two equal oral doses twice nightly. The first dose is administered prior to bedtime with the second dose requiring the patient to wake 2.5-4 hours later to take a second dose (Xyrem® U.S. Package Insert 2018), which is inconvenient and may jeopardize sleep structure architecture and sleep quality. Requiring a second nightly dose may also affect compliance, resulting in decreased efficacy and poorer quality of life. Additionally, the second dose can result in adverse events in the middle of the night, ranging from nausea/vomiting (potentially increasing aspiration risk) to falls (increasing fracture risk). Leaving a prepared, unattended second dose out in the middle of the night also poses a risk of misuse as it could be taken by others (i.e., college students, roommates, children, etc.) living with the intended user. Flamel Ireland Limited dba Avadel Ireland (Avadel) is developing FT218, an extended-release formulation of sodium oxybate that allows for a single dose prior to bedtime that mitigates the

need to interrupt sleep to take a second dose and potentially provides a safer alternative by avoiding middle of the night dosing and associated adverse events.

2. SERIOUS /LIFE-THREATENING CONDITION

2.1. Symptoms of Narcolepsy

The hallmark symptom of narcolepsy is EDS and is hence required for the diagnosis . It is also the most troublesome symptom and the one for which patients most commonly seek treatment. EDS is defined as the inability to stay awake and alert during the day, resulting in periods of involuntary sleep episodes or unintended lapses into "drowsiness" during activities of daily living (Thorpy 2012). In narcolepsy, EDS can exist despite adequate nighttime sleep. The chronic and severe nature of EDS predisposes these patients to deficits in multiple areas of functioning. When alertness is compromised, performance may be diminished across a variety of cognitive functions, work-related safety may be compromised, and productivity and overall quality of life may suffer. It is possible that performance deficits may precipitate reduced patient-reported quality of life and difficulty with achievement in work and/or school. Beyond this, the sleepiness can be so omnipresent as to cause patients to socially withdraw, making relationships with family and friends difficult to maintain and potentially strained.

Cataplexy, in the presence of EDS, is suggestive of type 1 narcolepsy and an indication for objective testing to confirm the diagnosis (Sansa et al. 2016). Cataplexy is defined as a sudden muscle weakness episode and can affect a few muscles (for example, facial muscles) or all skeletal muscles at once (Dauvilliers et al. 2014). As a result of the muscle weakness, patients momentarily have head nodding from weakness in the neck muscles, sagging of the jaw, buckling of the knees, dropping of objects from hands, and/or dysarthria or inability to speak during the episode. Sometimes they may slump or fall forward onto the ground, either all at once or more gradually.

Cataplexy attacks are typically brief, on average, lasting from milliseconds to 1-2 minutes. Cataplexy is typically triggered by emotions, most often by telling or hearing a joke, laughing, or becoming angry. These emotions have been combined to successfully identify cataplexy among cases and lack of cataplexy among controls with remarkable specificity. At initial presentation and close to symptom onset, and especially in children and teenagers, the onset of a cataplexy attack may not be precipitated by an emotional trigger and can happen almost spontaneously, termed then atypical cataplexy. It is unclear as to how and why the frequency or severity of cataplexy varies across patients and may or may not change over time (Dauvilliers et al. 2014).

The onset of cataplexy typically occurs after the onset of EDS. Less frequently it can occur years after the EDS. Aside from the emotional triggers for cataplexy attacks, withdrawal from rapid eye movement (REM)-suppressing drugs may also cause them (Dauvilliers et al. 2014).

DNS is the second most common symptom among narcolepsy patients after EDS (Mitler 1994). The DNS observed in narcolepsy is distinct from that seen in insomnia. While patients with insomnia have difficulty falling asleep at the beginning of the night and after nocturnal awakening, patients with narcolepsy fall asleep faster than insomniacs and even the general population. DNS in narcolepsy is characterized by frequent brief awakenings or shifts to lighter stages of sleep during the sleep period that are transient, with increased Stage 1 sleep, and

reduced deeper stages of sleep. Often this leaves patients feeling poorly rested or that their sleep was not refreshing. The contribution of DNS to the EDS in narcolepsy is not well understood.

Additional symptoms completing the narcolepsy pentad include hypnagogic/hypnopompic hallucinations (HH) (vivid dreams at sleep onset or offset that are more often associated with negative emotions) and sleep paralysis (feeling unable to move the body during transition periods of sleep; SP) (Roth et al. 2013). These may occur simultaneously and are often frightening to the patient. More specific for narcolepsy is their occurrence at sleep onset. Like cataplexy, SP and HH are REM-related phenomena. Thus, experiencing them at sleep onset is rare in the general population.

3. BASIS FOR UNMET MEDICAL NEED

3.1. Disadvantages of Currently Available Treatments

No cure exists for narcolepsy to date. Current treatments are symptomatic and are not directed towards any known pathophysiological target. Available treatments include wake-promoting agents (stimulants or sympathomimetics, modafinil, armodafinil, pitolisant, solriamfetol) which treat EDS, REM-suppressing drugs (tricyclic antidepressants [TCAs], serotonin and norepinephrine reuptake inhibitors [SNRIs], selective serotonin re-uptake inhibitors [SSRIs], monoamine oxidase inhibitors [MAOIs]) to treat cataplexy as well as HH and SP, and sodium oxybate which is effective for EDS and cataplexy as well as all other accessory symptoms. The severity of symptoms can vary greatly from one patient to another and, thus, the response to any given medication similarly varies from patient to patient.

Wake-promoting agents (e.g., modafinil, armodafinil, methylphenidate, dextroamphetamine, methamphetamine, pitolisant, solriamfetol) improve EDS in narcolepsy (Barateau et al. 2016, Roth et al. 2013, Sangal 1992). In diagnosed patients, modafinil and armodafinil (the more potent R-enantiomer of modafinil, not available in Europe) are often the first-line treatments prescribed to reduce EDS. In the absence of response to modafinil, methylphenidate is an effective second-line treatment for EDS. Amphetamines are potential alternatives for patients who do not respond satisfactorily to the first- and second-line stimulant options. Pitolisant is a treatment option approved in the U.S. in 2019 that belongs to a novel drug class and is indicated for the treatment of EDS in patients with narcolepsy as first or second choice. Solriamfetol is a dopamine and norepinephrine reuptake inhibitor (DNRI) that is another treatment option approved in the U.S. in 2019 indicated to improve wakefulness in adult patients with EDS with narcolepsy or obstructive sleep apnea. Some patients may need a combination of drugs or a mixture of short- and longer-acting medications for optimal treatment. This is evident by the fact that stimulants improve EDS, but they do not normalize it, as confirmed by patient reports in systematic studies (Nishino 2008, Xyrem® International Study Group 2005). Importantly, in previous Xyrem® (twice-nightly sodium oxybate) studies, up to 83% of patients who entered the study were on concomitant stimulants, yet still needed additional treatment for excessive daytime sleepiness and met stringent entry criteria for having persistent excessive daytime sleepiness despite stimulant use (U.S. Xyrem® Multicenter Study Group 2002). Similarly, in our Phase 3 study, patients were allowed to enter the study on stable doses of stimulants. At Baseline, well over half of the patients were on concomitant stimulants yet still had severe excessive daytime sleepiness as evident by Baseline MWT less than 11 minutes and ESS >10.

1.7.1 Fast Track Designation

Potent REM-suppressing antidepressants (i.e., SNRIs, SSRIs, TCAs and MAOIs) are used to treat cataplexy as well as HH and SP; however, the efficacy of these drugs in treating cataplexy has not been established in controlled clinical studies and their use (based on experience from off-label use) has not been approved by any regulatory agency.

Despite the number of therapeutic options, narcolepsy medications are often not fully effective and multiple treatments, such as antidepressants to treat cataplexy and one or more wake-promoting agent to treat EDS, are often required to address the variety of symptoms in narcolepsy (Abad and Guilleminault 2017). This increases the complexity of dosing regimens, likelihood of noncompliance and adverse events, and potential for drug interactions. Many patients have also had to give up beneficial treatments because of intolerable side effects or because they developed tolerance. Particularly, rebound cataplexy has been observed with the discontinuation of antidepressant therapy and it may last for several weeks. The use of stimulants can cause abuse or dependence in addition to tachycardia, urinary retention, and increased anxiety in some individuals (Mignot 2012). These adverse effects can deter patients from adhering to a multiple-treatment approach. Thus, there remains a need for new treatments that are safer, with simpler dosing regimens.

3.2. Comparison of FT218 to Approved Sodium Oxybate Formulations

Although these above treatments can be combined to treat the symptoms of narcolepsy, sodium oxybate can be a first-line treatment for both excessive daytime sleepiness and cataplexy in narcolepsy, while all other agents are indicated for one symptom or the other. Additionally, sodium oxybate is effective to treat the other accessory symptoms of narcolepsy, including HH, SP, and disturbed sleep (Bhattarai and Summerall 2017). Sodium oxybate (Xyrem®) is approved in the U.S. for the treatment of cataplexy in adults and for patients seven years of age and older with NT1, as well as for EDS in both types of narcolepsy. However, the twice nightly dosing regimen for Xyrem® is inconvenient, disrupts continuous sleep, can result in poor compliance which could lead to worsening efficacy and quality of life, and is associated with additional adverse events in the middle of the night both resulting from waking up from a deep sleep state as well as a second, high C_{max}.

Individuals suffering from fragmented sleep and an overall sleep deficit consider the elimination of the need to carefully time and wake up for a second nighttime dose to be a substantial advancement in therapy. In a survey of 1350 individuals impacted by narcolepsy, the results of which were distributed at the September 24, 2013 FDA Meeting on Drug Development for Narcolepsy, responses to a question about an ideal therapy included, “a drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require one dose taken at bedtime resulting in 8 hours of restorative sleep” (Unite Narcolepsy 2013).

FT218 is a once-nightly extended-release formulation of sodium oxybate that obviates the need for awakening during the night to take a second dose. REDACTED

REDACTED

Figure 1: Mean Plasma GHB Concentration (µg/mL) – Time Profiles after a Single Oral Administration of 6 g of FT218 or Two 3 g Administrations of Xyrem®

REDACTED

FT218 obviates the need for middle of the night awakening for a second nightly dose which could result in improvement in patient efficacy, safety, compliance and misuse. TREDACTED

3.2.1. Compliance Issues Related to Second Dose

Xyrem® has a short half-life (0.5-1 hour) and a duration of action of only 2-4 hours necessitating twice-nightly dosing in order to achieve 6-8 hours of nighttime sleep (Mignot 2012). Patients who consume a dose at bedtime are required to awaken and take another dose in the middle of the night. Current labeling for Xyrem® states that patients may need to set an alarm to awaken for the second dose. If the window for the second dose (2.5-4 hours after the first dose) is missed, patients are instructed to skip the second dose because of the potential substantial negative effects of a late second dose on functioning/alertness the following day.

REDACTED

1.7.1 Fast Track Designation

REDACTED

REDACTED

1.7.1 Fast Track Designation

REDACTED

1.7.1 Fast Track Designation

REDACTED

The need to set an alarm for a second nighttime dose also disrupts the sleep of roommates and partners who share a bedroom with an affected individual. A parent or caregiver may be adversely impacted by the need for nighttime dosing and burdened by concern that the patient will not reliably awaken. REDACTED

Therefore, not only does waking up in the middle of the night affect the patient, it also decreases the quality of life of their bed-partner. A once-nightly formulation of sodium oxybate would eliminate this issue for partners and caregivers.

REDACTED

REDACTED

REDACTED

3.2.2. Risk of Nocturnal Falls and Other Adverse Events Associated with Second Dose

Administration of a second nightly dose of Xyrem® presents safety risks. First, forcibly waking up from a sodium oxybate-induced deep sleep poses additional safety risks as one may get out of bed, ambulate and fall with subsequent injury resulting from a drug-induced groggy or stuporous state. Secondly, because of the rapid onset of effects, individuals are at risk of falls or other accidental injuries if the second dose is not consumed in bed (as is recommended in the label instructions). This risk was acknowledged by the FDA in a 2013 review of the Xyrem® post-

marketing data and was addressed by revision to the labeling language to address the risk of nocturnal falls. The label was updated to specify that patients should remain in bed following ingestion of the second dose; the prior version of the label already included these instructions with respect to the first dose.

Avadel reviewed FDA's Adverse Event Reporting System (FAERS) data for Xyrem® cases from 2003 through September 30, 2019. There have been 1957 cases including the adverse event of fall and any other event, 625 cases including adverse events of fall and fracture, and 35 cases of fall as the only adverse event. Through the Freedom of Information Act (FOIA), Avadel requested individual cases from the FDA related to falls and fracture with event dates ranging from 2016-2019. All cases requested were determined to be serious, indicated that Xyrem® was the suspect product, and were reported by healthcare professionals. To date, Avadel has reviewed 36 cases (12 requested per month) and 4 cases have adverse events linked to the second nightly dose of Xyrem®. Three patients got out of bed and fell, one breaking her wrist, one broke three bones in her face, and the third fractured her ankle. The fourth case involved a patient that passed out in the middle of the night after taking her second dose of Xyrem®.

In the real-world study mentioned above, Side Effects & Safety was the second highest

REDACTED

REDACTED

In addition, a meta-analysis of six studies conducted to assess the pharmacokinetics of FT218 in healthy volunteers found that, in general, known adverse events associated with sodium oxybate (i.e., neurological and gastrointestinal) occurred close to T_{max}, around the C_{max} period (approximately 1.5-2.0 hours after dosing) (Seiden et al. 2020). Since it appears that the AEs were related to C_{max} and FT218 has only one C_{max} compared to Xyrem®, it is hypothesized that FT218 will have a more favorable safety profile compared to twice-nightly dosing by avoiding a second C_{max} and the types of AEs described above.

REDACTED

1.7.1 Fast Track Designation

REDACTED

3.2.3. Risk of Misuse Associated with Second Dose

The Xyrem® instructions for use direct patients to measure out both nightly doses prior to bedtime and place the second dose near the bed for consumption 2.5-4 hours after the first dose. Although a container with child-resistant cap is provided for the second dose, there is the potential for consumption of the product left on a bedside table by a child while the parent is sleeping – if the child-resistant container is not used – or deliberate misuse by another person in the household. REDACTED

3.2.4. Potential Impact on Diversion

Sodium oxybate has a history of illicit use as the "date-rape drug." This substance has been added to a target's drink without his/her knowledge in order to incapacitate the individual. REDACTED

3.2.5. Food Effect

REDACTED

1.7.1 Fast Track Designation

REDACTED

3.2.6. Summary

The availability of once-nightly FT218 has the potential to eliminate the obvious disadvantages associated with twice-nightly sodium oxybate, including:

1. The need to disrupt patient and bed-partner/caregiver sleep in order to take a drug designed to promote sleep
2. The potential for safety events (e.g. falls) associated with middle of the night dosing related to waking up from a GHB-induced sleep as well as a second, larger C_{max} that is associated with other adverse events (nausea/vomiting)
3. The potential for decreased efficacy if the second dose is missed
4. The potential for less efficacy resulting from eating too close to dosing
5. The potential for misuse by leaving the second dose unattended at the bedside

4. DEVELOPMENT PLAN

REDACTED

REDACTED

5. CONCLUSION

As described above, narcolepsy is a serious condition associated with significant morbidity that has substantial impact on day-to-day functioning. While treatments do exist, none have fully met all of the needs of the patient population in a convenient dosing regimen. Avadel is developing a once-nightly sodium oxybate formulation that is expected to have comparable efficacy to the currently approved Xyrem® (when dosed as recommended), but will address major compliance and safety issues associated with the necessity to take a second dose in the middle of the night, as well as potentially reducing misuse/diversion of the product. As such, Avadel is requesting Fast Track designation for FT218 on this basis.

6. LIST OF RELEVANT DOCUMENTATION TO SUPPORT DESIGNATION REQUEST

Seiden D, Grassot J, Monteith D, and Dubow J. The Pharmacokinetic-Adverse Event Relationship For FT218, a Once-Nightly Sodium Oxybate Formulation. Accepted to the American Academy of Neurology Annual Meeting, April 25 – May 1, 2020, Toronto, CA.

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APPENDIX A. THE PHARMACOKINETIC-ADVERSE EVENT RELATIONSHIP FOR FT218, A ONCE-NIGHTLY SODIUM OXYBATE FORMULATION (SEIDEN ET AL. 2020)

The Pharmacokinetic-Adverse Event Relationship For FT218, a Once-Nightly Sodium Oxybate Formulation

Seiden D, Grassot J, Monteith D, Dubow J

Objective
To evaluate the pharmacokinetic-adverse event (AE) relationship for FT218, an investigational once-nightly sodium oxybate formulation.

Background
Sodium oxybate is an effective treatment for excessive daytime sleepiness and cataplexy in patients with narcolepsy. The approved formulation requires twice-nightly dosing: at bedtime and 2.5 – 4 hours later, which results in two distinct Cmax's. FT218 is a controlled-release formulation of sodium oxybate intended for once-nightly dosing, using Avadel's proprietary Micropump™ technology.

Design/Methods
Six single-dose, randomized, crossover studies that assessed the pharmacokinetics of FT218 at 4.5, 6, 7.5 and 9 g in healthy voluntters were used in this analysis. Lattice plots, "spaghetti" plots, and scatter plots of individual gamma hydroxybutyrate concentrations and indicators when AEs by system, organ, or class (SOC) were created to determine any PK-AE relationship.

Results
A total of 129 healthy volunteers received single doses of FT218 between 4.5 – 9 g. Most AEs, specifically for the neurological and gastrointestinal SOC, occurred close to T_{max}, during the C_{max} period, which for FT218 was around 1.5-2 hours after dosing. These AEs were known AEs associated with sodium oxbyate. There appeared to be no clear correlation between individual plasma GHB concentrations levels and AEs between subjects. Individual AEs were equally distributed above and below the mean population C_{max} and AUC_{inf} for the dataset.

Conclusion
In general, adverse events for FT218 occurred around T_{max}. There was no clear population toxicokinetic range for when AEs occur with FT218, but mostly individual thresholds. Since it appears AEs are related to C_{max}, and FT218 only has one C_{max} compared to two with the currently available product, it is hypothesized that FT218 will have a favorable safety profile compared to twice-nightly dosing. The efficacy and safety of FT218 for the treatment of excessive daytime sleepiness and cataplexy in narcolepsy patients is currently being evaluated in the Phase 3 REST-ON pivotal study.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW

RULE 7.1.1 CERTIFICATION

Pursuant to D. Del. LR 7.1.1, counsel for the parties met and conferred regarding Defendant's foregoing motion, including verbally by teleconference with Delaware counsel, and the parties were unable to reach an agreement on the relief sought therein.

Dated: September 12, 2022

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

JAZZ PHARMACEUTICALS, INC., Plaintiff, v. AVADEL CNS PHARMACEUTICALS, LLC, Defendant.	C.A. No. 21-691-GBW

[PROPOSED] ORDER REGARDING AVADEL'S MOTION TO EXPEDITE

This _____ day of _____, 2022, upon consideration of Defendant Avadel CNS Pharmaceuticals, LLC Motion to Expedite Consideration of Avadel's Renewed Motion for Partial Judgment on the Pleadings (the "Motion to Expedite"), IT IS HEREBY ORDERED THAT:

1. The Motion to Expedite is GRANTED.
2. The Court will expedite consideration of Avadel's pending Renewed Motion for Judgment on the Pleadings pursuant to Fed. R. Civ. P. 12(c) (D.I. 117) (the "Rule 12(c) Motion") and issue a ruling as soon as possible.
3. The Court will hold a [telephonic/in-person] conference on September ___, 2022 at _____ a.m./p.m. to address the Rule 12(c) motion, and to the extent necessary, any related claim construction disputes for U.S. Patent No. 8,731,963 (the "'963 patent").

_____
UNITED STATES DISTRICT JUDGE

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on September 12, 2022 on the following counsel in the manner indicated below.

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