No. 18-2086

In the United States Court of Appeals for the First Circuit

IN RE: LANTUS DIRECT PURCHASER ANTITRUST LITIGATION

FWK HOLDINGS, LLC and CESÁR CASTILLO, INC.,
Plaintiffs-Appellants,

v.

SANOFI-AVENTIS U.S. LLC,
Defendant-Appellee.

On Appeal from the United States District Court
for the District of Massachusetts

PLAINTIFFS-APPELLANTS' BRIEF

THOMAS M. SOBOL
KRISTIE A. LASALLE
KRISTEN A. JOHNSON
HAGENS BERMAN SOBOL SHAPIRO LLP
55 Cambridge Parkway, Suite 301
Cambridge, MA 02142
(617) 482-3700
tom@hbsslaw.com

MATTHEW W.H. WESSLER
JOSHUA MATZ
GUPTA WESSLER PLLC
1900 L Street, NW
Washington, DC 20036
(202) 888-1741
matt@guptawessler.com

March 15, 2019

Counsel for Appellants

CORPORATE DISCLOSURE STATEMENT

Pursuant to Federal Rule of Appellate Procedure 26.1, the appellants state as follows.

Appellant FWK Holdings, LLC has no parent corporations, and no publicly held company owns 10% or more of its stock.

Appellant Cesar Castillo, Inc. has no parent corporations, and no publicly held company owns 10% or more of its stock.

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REASONS WHY ORAL ARGUMENT SHOULD BE HEARD

More than 100 million Americans—one in three—currently live with diabetes or pre-diabetes. Although insulin has been widely used to treat diabetes for nearly a century, in the absence of competition the price for this drug has spiked, tripling over the last fifteen years and leading many to engage in dangerous self-rationing. This case involves an effort to hold one insulin manufacturer accountable for its anticompetitive scheme to exclude competition from, and unlawfully maintain its monopoly power over, the multi-billion dollar insulin glargine market. Because this appeal raises significant questions at the intersection of antitrust and patent law that will affect important matters of public health and access to life-saving drugs, oral argument is warranted.

INTRODUCTION

Under the Hatch-Waxman Act, a company seeking FDA approval to sell a brand-name drug must list "any patent which claims the drug" in the Orange Book, a publicly available catalog identifying the patents protecting brand-name drugs. *See* 21 U.S.C. § 355(b)(1). As the FDA's implementing regulations instruct, this statutory requirement restricts Orange Book listing to only those patents that claim the drug's "active ingredient" or that claim "a finished dosage form" (like a tablet or a capsule) that "contains" the drug's active ingredient. 21 C.F.R. § 314.53; *Id.* § 314.3.

This case arises from Sanofi's decision to disregard that plain-text statutory requirement. When Sanofi first sought approval in 2000 for its blockbuster diabetes drug insulin glargine, marketed as Lantus, it submitted the '722 patent claiming this drug for Orange Book listing. By listing the patent, Sanofi obtained a legitimate monopoly over insulin glargine products until its '722 patent expired in 2014. At that point, other companies should have been able sell insulin glargine products, thus introducing competition into the market and driving down the drug's supra-competitive cost.

That is not what happened. Shortly before its '722 patent expired, Sanofi began listing additional patents in the Orange Book under Lantus. Chief among them was the '864 patent, which claimed a "drive mechanism" component that

can be used in numerous non-drug-specific drug delivery devices. But as the district court correctly found (and as a review of the patent readily confirms), the '864 patent "itself does not mention," let alone claim, either insulin glargine or a finished dosage form containing that drug. Add. 10. Instead, all it claims is one component, among many, of an injector pen that Sanofi later sold pre-filled with several different drugs, including Lantus. Because the '864 patent does not satisfy the statutory or regulatory criteria, it should not have been listed in the Orange Book.

The antitrust laws impose liability for this unlawful conduct. As the district court recognized, "improperly listing a patent" in the Orange Book "may subject the patent holder to antitrust liability" under the Sherman Act. Add. 18. That is because an improper Orange Book listing enables manufacturers to maintain their monopoly power beyond when competitors should have been allowed to enter the market. And, as alleged here, that is exactly what happened following Sanofi's decision to the '864 patent, which was not set to expire until 2024. By listing the '864 patent, Sanofi could—and did—sue would-be competitors who tried to enter the insulin glargine market when the '722 patent approached expiration. Under Hatch-Waxman, the mere filing of those suits automatically triggered a stay of the FDA's approval of the competitors' applications. This extended Sanofi's

market exclusivity for months beyond when competitors should have been able to enter. During this delay, Sanofi sold more than $11 billion of Lantus at a premium.

In dismissing the purchasers' antitrust claims, the district court twice refused to apply Hatch-Waxman's plain-language requirements to the '864 patent. Relying on commentary in an FDA rulemaking and several industry follow-up letters, it reasoned that the Orange Book listing rules contained a "significant ambiguity" over whether a manufacturer could list patents "relating to" an approved drug—even if the patents do not claim the active ingredient or a dosage form containing it. Add. 22. The district court further held that, even if the listing was improper, antitrust liability exists only if a manufacturer's patent listing was "objectively baseless." Add. 21.

Neither holding is correct. The text of section 355(b)(1) and its implementing regulations is clear and unqualified: only patents that claim the drug, or a dosage form containing it, may be listed. Patents that claim aspects of a product that "are distinct from the drug product . . . fall outside the requirements for patent submission" and "must not be submitted." 68 Fed. Reg. 36676, 36680 (June 18, 2003). The '864 patent not only claims a distinct invention; it fails to reference the drug at all. Moreover, the court's "objectively baseless" standard is itself objectively baseless. It rests on nothing more than *ipse dixit* from another district court that mistakenly lifted this rule from an element of the *Noerr-Penington* analysis. Under

familiar antitrust principles, if a drug manufacturer's improper listing extends its monopoly, the company faces antitrust liability regardless of whether its listing was "reasonable."

Hatch-Waxman's structure and purpose reinforce this straightforward understanding. When Congress created the Orange Book listing process, it struck a balance between incentivizing innovation and expediting the entry of non-infringing competitor drugs. Although listing a patent in the Orange Book confers a near-automatic period of market exclusivity, the types of patents that can trigger this lucrative exclusivity are intentionally cabined to only those that actually claim the drug or a dosage form containing the drug. And because the FDA's role in facilitating Orange Book listings is purely "ministerial," the agency has specifically recognized that the safeguard against improper Orange Book listings is precisely what the drug purchasers seek—private enforcement of the antitrust laws in federal court.

In short, the decision below contravenes Hatch-Waxman's plain text, upsets its careful balance, and effectively immunizes those drug manufacturers that might be tempted to unlawfully list patents. This Court should reverse.

JURISDICTIONAL STATEMENT

The district court had subject-matter jurisdiction under 28 U.S.C. §§ 1331(a) and (d), 1337(a), and 15 U.S.C. § 15. The court issued a final judgment granting

Sanofi's motion to dismiss with prejudice on October 24, 2018. Add. 33-62; JA855. The appellants appealed on October 29, 2018. JA856. This Court has jurisdiction under 28 U.S.C. § 1291.

STATEMENT OF THE ISSUES

1. Did the district court err in holding that 21 U.S.C. § 355(b)(1) and 21 C.F.R. § 314.53(b) are ambiguous as to whether the '864 patent—which does not claim insulin glargine or any other drug product—could be listed in the Orange Book?

2. Did the district court err in holding that liability for an improper Orange Book listing depends on whether such listing was "unreasonable" or "objectively baseless"?

STATEMENT OF THE CASE

I. Regulatory background

A. The Hatch-Waxman Act.

A company seeking to market a new brand-name drug must undergo a "long, comprehensive, and costly" process, including conducting clinical trials, and present its results to the FDA in a New Drug Application (NDA). *FTC v. Actavis, Inc.*, 570 U.S. 136, 142 (2013); *see* 21 U.S.C. § 355(a)-(b).

Before 1984, companies seeking to market competitor drugs had to follow the same process. The expense of this process deterred many companies from even

trying, resulting in "the practical extension of the [brand-name drug's] monopoly position . . . beyond the expiration of the patent"—to the detriment of purchasers. H.R. Rep. No. 98-857, pt. 2, at 4 (1984). By the early 1980s, the anticompetitive effects had become so severe that purchasers had no alternatives to at least 150 brand-name drugs whose patents had expired or were otherwise unenforceable. *Id.*, pt. 1 at 17 (1984).

Congress tackled this problem in the Hatch-Waxman Act. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585. With Hatch-Waxman, Congress worked to strike a "balance" between "two competing interests." 68 Fed. Reg. at 36676. On one hand, it sought to encourage "research and innovation by protecting the patent interests of the patent owner and innovator drug company." *Id.* On the other, it endeavored to promote competition by expediting the entry of non-infringing competitors into pharmaceutical drug markets in order to decrease healthcare costs for consumers. *See* H.R. Rep. No. 98-857, pt. 1, at 14 (noting that speeding competitor drugs to market would make available "more low cost" drugs).

Congress achieved this balance in two ways. First, it created a set of separate but related pathways governing the approval of new and competitor drugs. And second, it established a framework for protecting drug patents that grants

innovators a period of lawful patent exclusivity while incentivizing would-be competitors to challenge or design around weak or invalid patents.

B. The drug-approval process.

Under Hatch-Waxman, a drug manufacturer seeking to market a new brand-name drug must obtain FDA approval before selling the drug in the United States. 21 U.S.C. § 355(b)(1). In addition to presenting the FDA with clinical data, safety information, and detailed manufacturing plans, an applicant must also select the final dosage form of its proposed drug from a list of dosage forms published by the FDA. *See* 21 C.F.R. § 314.50. That list includes both well known drug forms like "tablet[s]" and "injectables," as well as less common drug forms like shampoos and pre-filled delivery systems. *See Approved Drug Products with Therapeutic Equivalence Evaluations* at Appendix C (39th ed. 2019) (listing dosage forms). If the NDA demonstrates that a drug is safe and effective for its intended use, the FDA will approve the application. 21 U.S.C. § 355(c)(1)(A), (d).

After NDA approval, a company seeking to make any "major changes" to its product must submit a supplemental NDA (sNDA). 21 C.F.R. § 314.70(b). sNDAs are required for changes in "inactive ingredients," *id.* § 314.70(b)(2)(i), and changes to the "container closure system that controls the drug product delivered to a patient"—*e.g.*, changing the container from "vial to syringe," *id.* § 314.70(b)(2)(vi). If

a major change alters the drug product's dosage form, the sNDA must also identify the new dosage form. 21 C.F.R. § 314.71(b) (citing § 314.50); *id.* § 314.50(a).

Hatch-Waxman also created two new drug-approval pathways, simplifying the process for companies seeking to compete with brand-name drugs. First, a company may seek approval for a generic drug by filing an Abbreviated New Drug Application (ANDA). 21 U.S.C. § 355(j)(8)(B); *see Actavis*, 570 U.S. at 142. Or, as relevant here, a company may submit a "§ 505(b)(2) application"—an NDA citing studies that "were not conducted by or for the applicant . . . ." 21 U.S.C. § 355(b)(2). The application can rely on the FDA's prior "finding of safety and effectiveness" for another "listed drug" containing the same therapeutic ingredient (though not necessarily in the same dose, form, or route of administration). 21 C.F.R. § 314.54(a)(1)(iii).

C. The Orange Book listing process.

When Congress enacted Hatch-Waxman, it codified a new statutory patent submission and listing process that required drug manufacturers seeking approval for a new drug to publicly disclose information about the patents protecting the drug. This process exists for two reasons: *first*, "so that competitors understand the scope of the brand's ostensible patent protection," Add. 6; and *second*, so that the original drug manufacturer may immediately sue—and obtain a near-automatic

stay of competition—if another company challenges a patent protecting the drug. Add. 7.

1. The statutory framework. The submission and listing process is codified in 21 U.S.C. § 355(b)(1). A manufacturer seeking approval for a new drug must submit to the FDA information regarding "any patent which claims the drug for which the" company "submitted the application . . . and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." § 355(b)(1). This section also requires the FDA to publish all submitted patent information in its publicly available *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). *Id.*; *see* 21 C.F.R. § 314.53(e).

Alongside the Orange Book program, Congress created a mechanism to guide other drug manufacturers seeking to bring competitor drugs to market. *See* 21 U.S.C. § 355(j)(2)(A). Any would-be competitor must specifically address each Orange-Book listed patent for the original drug. § 355(j)(2)(A)(vii). The would-be competitor can certify that the original drug manufacturer has not listed any patents in the Orange Book, that the listed patents have expired, or that it will wait for the listed patents to expire before marketing its product. § 355(j)(2)(A)(vii)(I)-(III). Alternatively, the would-be competitor can submit a "paragraph IV" certification if the applicant believes the listed patents are "invalid, unenforceable, or will not be

infringed" by its competing product. § 355(j)(2)(A)(vii)(IV). If the would-be competitor submits a paragraph IV certification, it must notify the original drug manufacturer. *Id.* § 355(j)(2)(B).

Hatch-Waxman "treats the certification itself as a technical act of [patent] infringement." Add. 7; *see* 35 U.S.C. § 271(e)(2)(A). As a result, a company that receives a paragraph IV notice has standing to sue, 35 U.S.C. § 271(e)(2)(A), so long as it has a good-faith basis for believing that the competing product infringes its patents. *See Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365-66 (Fed. Cir. 2003). And, if the original manufacturer sues within 45 days, the FDA may not approve the would-be competitor's drug application for up to thirty months while the parties litigate the patent dispute. 21 U.S.C. § 355(c)(3)(C).

2. The regulatory framework. Pursuant to Hatch-Waxman, the FDA has twice engaged in rule-making to establish regulations governing the Orange Book listing process.

The 1994 rule. The FDA first promulgated regulations governing the Orange Book listing process in 1994. 59 Fed. Reg. 50338 (Oct. 3, 1994); 21 C.F.R. § 314.53. The FDA strictly adhered to the statutory requirements contained in § 355(b)(1). *See, e.g.*, 59 Fed. Reg. at 50343 (refusing to adopt requirements that would "go beyond" or run "contrary to" the statutory language or fail to "serve any statutory purpose"). The FDA "clarif[ied]" that Congress's decision restricting

Orange Book listing to only those patents that "claim[] a drug" encompasses patents that "claim a drug substance or drug product." 59 Fed. Reg. at 40343. The agency thus established the following regulation for companies submitting patents for Orange Book listing:

> (b) Patents for which information must be submitted.
>
> An applicant . . . shall submit information on each patent that claims the drug or a method of using the drug that is the subject of the new drug application or amendment or supplement to it and with respect to 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. For purposes of this part, such patents consist of drug substance (ingredient) patents, drug product (formulation and composition) patents, and method of use patents. . . . For patents that claim a drug substance or drug product, the applicant shall submit information only on those patents that claim a drug product that is the subject of a pending or approved application, or that claim a drug substance that is a component of such a product . . . .

59 Fed. Reg. at 50363.

The FDA also declined to establish a mechanism for agency review of patents listed in the Orange Book. Because the FDA "does not have the resources or the expertise to review patent information for its accuracy and relevance," it concluded that its "scarce resources would be better utilized in reviewing applications rather than reviewing patent claims." 59 Fed. Reg. at 50343. Instead, the agency required a brand manufacturer to execute a declaration that the submitted patent "covers the formulation, composition, and/or method of use" of

the listed drug, § 314.53(c)(2)(i). *Id.* It concluded that the "declaration requirements," coupled with "an applicant's potential liability if it submits an untrue statement of material fact, will help ensure that accurate patent information is submitted." 59 Fed. Reg. at 50345.

The 2003 rule. In 2003, the FDA revised its Orange Book listing regulations. *See* 68 Fed. Reg. at 36676. The agency still aimed to preserve the "balance between the innovator companies' intellectual property rights and the desire to get [competitor] drugs on the market in a timely fashion." *Id.* But it made several changes to "reduce confusion" over, and "curb attempts to take advantage of," the listing requirements. *Id.*

First, the agency confirmed that only those patents claiming either the drug substance or the drug product of a pending or approved application could be listed in the Orange Book. *See id.* at 36703-04. It clarified that, for patents claiming the drug substance, the patent must specifically claim either the "drug substance that is the subject of the pending or approved application" or "a drug substance that is the same as the active ingredient that is the subject of the approved or pending application." *Id.* The FDA also instructed that, for patents claiming the drug product, the patent's claim must fall within the definition of "drug product" set forth in 21 C.F.R. § 314.3. 68 Fed. Reg. at 36704. Section 314.3, in turn, defined

"drug product" as "a finished dosage form"—including a "tablet, capsule, or solution"—that "contains a drug substance." § 314.3(b).

Second, in addition to reiterating which patents must be listed in the Orange Book, the FDA specified which types of patents must not. One such prohibited type is "patents claiming packaging." § 314.53(b)(1). These patents were not permitted to be listed because, unless they claim the drug product, they "fall outside of the requirements for patent submission." 68 Fed. Reg. at 36680 ("Such packaging and containers are distinct from the drug product."). "[O]nly patents meeting the statutory requirements" can be submitted for listing. *Id.* at 36683.

Some commenters suggested that certain packaging or device patents, like "metered dose inhalers and transdermal patches," should be allowed because they "are drug delivery systems used and approved in combination with a drug." *Id.* at 36680. In response, the FDA drew a clear distinction: a packaging or device patent could be listed in the Orange Book only if it *also* "claims the drug product as defined in § 314.3." *Id.* The "key factor," in short, "is whether the patent being submitted claims the finished dosage form of the approved drug product." *Id.* So, a patent does not claim a pre-filled drug delivery system (or any other final dosage form) unless it also claims the drug's active ingredient. *Id.*

Third, the FDA reaffirmed that it would not police Orange Book listings. It made clear that its "patent listing role remains ministerial." *Id.* at 36683. And it

refused to "create a new process for de-listing patents" or otherwise engage in a "substantive" review of listed patents. *Id.* Not only would an "administrative process for reviewing patents" fall "outside both [the FDA's] expertise and [its] authority," but it could frustrate the agency's goal of "assur[ing] that . . . ANDAs or [section] 505(b)(2) applications would be approved sooner." *Id.* Staying out of the listing process, moreover, would reinforce "[a] fundamental assumption of the Hatch-Waxman Amendments"—that "the courts are the appropriate mechanism for the resolution of disputes about the scope and validity of patents." *Id.*

Post-2003 manufacturer petitions. After the FDA's 2003 final rule, a number of brand-name drug manufacturers petitioned the FDA to expand the scope of patents permissibly listed in the Orange Book. *See* JA860-96. These companies asked the FDA to agree that "patents claiming an approved pre-filled drug delivery system" could be listed in the Orange Book—"even if" the patents do not actually claim the drug substance, or a dosage form containing the drug substance. JA882.

In the companies' view, listing such patents would help competitors because the patents might not otherwise be discovered "if they are not listed in the Orange Book." *Id.* Some manufacturers informed the FDA that they believed that "the term 'pre-filled drug delivery system' encompasses, among other things, pre-filled syringes approved to deliver an approved drug product"—and that "patents directed to such drug delivery systems" could be listed "even if the patents disclose

but do not claim, or neither disclose nor claim, the active ingredient or formulation of the approved drug product." *Id.*; *see also* JA884.

The FDA did not alter its regulations in response to these petitions. Instead, in interim responses reflecting its statutory obligation to respond within a fixed period, the FDA noted that, "given the numerous demands on the Agency's resources" and "the need to address other Agency priorities," it had "not yet resolved the issues raised" by the request for an advisory opinion and was "unable to reach a decision." *See, e.g.*, JA895.

II. Factual background

A. Sanofi develops and markets a blockbuster diabetes drug called insulin glargine.

Insulin is a peptide hormone found in the pancreas. Although it has been widely used to treat diabetes for nearly a century, two types of synthetic insulin drugs now dominate the market. JA63-65. These drugs are known as "rapid-acting" insulin and "long-acting" insulin, and three brand-name manufacturers—Eli Lilly, Novo Nordisk, and Sanofi—have long controlled their commercial sale. JA63-65. By frequently "tweak[ing] their formulations," these manufacturers have secured extended patent protection over their drugs and, in turn, hold a near complete monopoly over the insulin markets. *See* Danielle Ofri, Op-Ed, *The Insulin Wars*, N.Y. Times, Jan. 20, 2019, at SR4, http://nyti.ms/2S0R8xm; JA64.

This has contributed to the "exorbitant" price of insulin drugs over the last two decades. Ofri, *The Insulin Wars*, https://nyti.ms/2S0R8xm. Between 2002 and 2013, "prices tripled" for insulin, *id.*; the "typical cost for patients" increased from about $40 a vial (which lasts about a week or two) to $130—with some paying around $300. Randi Hutter Epstein & Rachel Strodel, *Diabetes Patients at Risk From Rising Insulin Prices*, N.Y. Times, June 22, 2018, https://nyti.ms/2JZeCzD. More than 100 million Americans—one in three— currently live with diabetes or pre-diabetes and, without any viable competition to drive prices down, dangerous insulin "self-rationing has become common." Ofri, *The Insulin Wars*, https://nyti.ms/2S0R8xm.

Insulin glargine is a long-acting genetically modified form of human insulin. JA63. Sanofi holds the original patent claiming this drug, known as the '722 patent. JA66. In 2000, the FDA approved Sanofi's Lantus NDA—the brand name of insulin glargine. JA66. At first, Lantus came in two forms: (1) vials from which insulin could be drawn with a disposable syringe, and (2) cartridges that snapped into a re-usable injector pen. JA67. Sanofi began marketing Lantus in May 2001 and, almost immediately, the drug achieved $1 billion-per-year blockbuster status. Less than three years later, Sanofi was selling $7.87 billion of Lantus a year. JA68-69. In 2017, the company made $11,000 per minute on Lantus. I-MAK, *Overpatented, Overpriced Special Edition: Lantus* at 3, 7 (Oct. 30, 2018).

B. Sanofi lists the '722 patent claiming insulin glargine in the Orange Book, giving it a monopoly over insulin glargine products until 2014.

When Sanofi filed its Lantus NDA, it designated the final dosage form of Lantus as an "injectable" from among the dosage forms listed in the Orange Book's Appendix. JA80. It also submitted the '722 patent—which specifically claimed insulin glargine—for listing in the Orange Book. JA66. That patent expired on August 14, 2014 and its regulatory exclusivity period ended February 12, 2015. JA66. Competitors should have been free to market other insulin glargine products in February 2015, introducing competition into the insulin glargine market and driving down costs. JA85.

C. Sanofi begins obtaining and listing other patents under Lantus in the Orange Book and delays competitors.

But several years after it first obtained approval to market and sell insulin glargine, Sanofi began accumulating other patents and linking them to Lantus. *See* JA85. First, Sanofi obtained two patents (the '652 and '930 patents) claiming the use of specific preservatives to prolong insulin glargine's shelf-life of. JA73. Although Lantus cartridges contained none of those preservatives, JA70, Sanofi listed the patents in the Orange Book for both vials and cartridges. JA74-75. That

gave Sanofi the ability to exclude competition until the last of these patents expired in January 2024.[1]

Next, Sanofi developed a new disposable injector pen device, called the SoloSTAR, and obtained several patents claiming components of that pen. JA78. Sanofi created the SoloSTAR to be a universal, non-drug-specific pen: it can be used with several drug categories, including "insulin, growth hormones, [and] low molecular weight heparins." Add. 85. Sanofi sells the SoloSTAR with multiple drugs, including Toujeo, Apidra, and Admelog. *See* JA76-77, JA117.

In 2006, Sanofi submitted an sNDA to the FDA to enable it to start selling insulin glargine in the SoloSTAR pen. JA70. Sanofi did not suggest that adding the SoloSTAR pen changed Lantus's final dosage form; insulin glargine remained an injectable but would be loaded into the SoloSTAR. *See* JA80, JA83, JA240. The only change would be in the "drug product container closure system that controls the drug product delivered to a patient." 21 C.F.R. § 314.70(b)(2)(vi); JA311 (FDA letter noting that the sNDA "provide[s] for the addition of disposable injector pens").

[1] Recently, the PTO's Patent Trial and Appeal Board invalidated both patents. *See* Press Release, Mylan N.V., Sanofi's Formulation Patents on Multibillion-Dollar Lantus® are Invalidated by U.S. Patent and Trademark Office via IPR, Announces Mylan (Dec. 13, 2018), https://bit.ly/2LlvgHf.

In 2007, the FDA categorized Sanofi's SoloSTAR sNDA as a change to Lantus's "Labeling-Container/Carton Labels, Labeling-Package Insert." JA72, JA171. Consistent with Sanofi's request, the agency treated the SoloSTAR pen as a container or packaging. JA70-71. For example, although the FDA called the SoloSTAR a "device," Add. 45, it explained that the SoloSTAR sNDA was a "packaging supplement," and determined that "the SoloStar cartridge holder . . . is considered secondary packaging," since "[n]o part of the SoloStar has contact with the drug product." JA71.

Sanofi then submitted several of the SoloSTAR patents to the FDA for listing in the Orange Book. JA84. Among these was the '864 patent, entitled "Drive Mechanisms Suitable for Use in Drug Delivery Devices," which Sanofi listed in the Orange Book. JA78-79, JA84. Because the '864 patent was not set to expire until 2024, listing it in the Orange Book extended Sanofi's monopoly over insulin glargine products for nine years beyond the expiration of the '722 patent claiming the drug insulin glargine. JA66, JA79, JA85.

The '864 patent does not claim the drug substance insulin glargine, Add. 69-94; indeed, it does not even mention Lantus or insulin glargine. Nor does the '864 patent claim a pre-filled drug delivery system containing insulin glargine. *Id.* The '864 patent contains the following ten claims:

- Claim 1 claims "[a] drive mechanism for use in a drug delivery device" with five attributes: "a housing having a helical thread," a

"dose dial sleeve," a "drive sleeve," a "piston rod," and a "clutch mechanism located between the dose dial sleeve and the drive sleeve;"

- Claim 2 claims a similar "drive mechanism," but without a piston rod;
- Claims 3 through 7 describe different ways of constructing claim 2's drive mechanism;
- Claim 8 claims the same "drive mechanism," with greater specificity as to how the attributes work together, and their mechanics; and
- Claims 9 and 10 claim variations on the descriptions in claim 8.

Add. 93; JA82-83.

D. Despite Sanofi's listing of additional patents in the Orange Book, other companies prepare to launch competitor insulin glargine drugs.

In late 2013, Lilly planned to enter the insulin glargine market. It filed a section 505(b)(2) application with the FDA, seeking approval to market an insulin glargine product, called Basaglar, using Lilly's own patented pen technology, the KwikPen. JA88-89. Because Lilly's application relied on studies conducted for Lantus, Lilly provided patent certifications for every patent listed in the Orange Book for Lantus SoloSTAR, including the '864 patent. *Id.* Lilly certified that it would wait to market its product until the '722 patent expired; but, since it proposed using a patentably distinct injector pen, JA93-96, Lilly submitted paragraph IV certifications as to each injector-pen patent, asserting its product would not infringe them. JA89; § 355(j)(2)(A)(vii)(IV).

Other competitors followed. In 2016, Merck submitted a section 505(b)(2) application, seeking permission to market another insulin glargine product,

Lusduna. JA109. By then, Sanofi's insulin glargine patent had expired, yet Merck was forced to file paragraph IV certifications regarding all of Sanofi's injector pen patents—even though none claimed, or even mentioned, insulin glargine. JA109-10. In 2017, Mylan also submitted a section 505(b)(2) application for its own insulin glargine product. JA115. Because Sanofi had listed even more Lantus-related patents in the Orange Book, Mylan had to file paragraph IV certifications for sixteen pen patents. *Id.*

E. Sanofi blocks these efforts by suing would-be competitors based on the vial formulation and pen patents that it listed in the Orange Book.

In January 2014, just three days after Sanofi received Lilly's paragraph IV certification, it sued Lilly for infringement based on its vial formulation and injector pen patents. JA92. As a result of the lawsuit, *see* 21 U.S.C. § 355(c)(3)(C), FDA approval for Basaglar was automatically stayed for 30 months, or until the conclusion of the litigation, whichever happened first. JA92. Sanofi sought to bar Lilly from manufacturing or selling its insulin glargine drug until all of its Lantus-related patents expired and Sanofi's period of exclusivity ended in 2024. On September 28, 2015, Lilly and Sanofi settled. Sanofi granted Lilly a royalty-bearing license to sell Basaglar and Lilly agreed to delay its entry until December 2016. JA103. After settling with Lilly, Sanofi sued Merck, and then Mylan, alleging similar infringement claims. JA110.

III. This case

A. Purchasers of insulin glargine products bring suit against Sanofi for anticompetitive conduct.

In an effort to curtail Sanofi's anticompetitive conduct, purchasers of insulin glargine brought a putative class action against the company. They alleged that the prices they paid for insulin glargine products were far higher than they should have been, and that these inflated prices flowed from Sanofi's illegal anticompetitive conduct—which served to delay competition in the insulin glargine market. JA120. The purchasers brought two claims under the Sherman Act, 15 U.S.C. § 2. *See* JA129-33 (alleging that Sanofi engaged in an unlawful scheme to monopolize, or attempt to monopolize, the market for insulin glargine products in violation of section 2 of the Sherman Act). These claims focused on Sanofi's scheme to improperly list multiple patents in the Orange Book and leverage them against would-be competitors. *Id.*

B. Sanofi files a motion to dismiss.

Sanofi sought to dismiss the claims. Sanofi acknowledged that "an improper Orange Book listing may subject a patent holder to antitrust liability," Mem. in Support of Mot. Dismiss 2d Amended Compl. 13, ECF No. 55, and it recognized that "the law *requires*" that drug manufacturers list patents in the Orange Book only "that claim[] an approved 'drug substance,' 'drug product,' or 'method of using such a drug,'" Mem. In Support of Mot. Dismiss 1st Amended Compl. 17, ECF

No. 22. But Sanofi insisted that "an objective analysis of the '864 patent" established that it "complied" with these "statutory and regulatory obligations." *Id.* at 1.

Sanofi also argued that, even if the '864 patent itself did not meet the specific listing requirements, it was properly listed in the Orange Book because it "relates to" a "pre-filled drug delivery system for insulin glargine." *Id.* at 19. Under Sanofi's theory, the "key question" was whether the components claimed by the '864 patent were used in a "drug delivery device" that itself met the definition of "drug product" under the Orange Book regulation. Because the "answer is clearly 'yes,'" Sanofi argued, there was nothing "improper" about submitting the '864 patent and listing it in the Orange Book. *Id.* Sanofi then went further, insisting that even if its arguments were not unambiguously correct, Sanofi had a "reasonable basis" for listing the '864 patent and so could not be held liable for its submission under the antitrust laws. *Id.* at 22 (quoting *Organon Inc. v. Mylan Pharm., Inc.*, 293 F. Supp. 2d 453, 460 (D.N.J. 2003))].

C. The district court dismisses the claims.

The district court adopted Sanofi's theory and held that the purchasers had "failed to sufficiently allege a claim" that Sanofi's patents were "improperly listed in

the Orange Book." Add. 3.[2] Although it agreed that "improperly listing a patent in the Orange Book may subject the patent holder to antitrust liability," it ruled that Sanofi's decision to list the '864 patent (and other pen patents) was "not improper." Add. 43.[3]

In reaching this conclusion, the court acknowledged that, by their terms, the relevant statutory and regulatory listing requirements restrict listing to only those patents that claimed either "the drug for which the applicant submitted the application," the drug substance, or the drug product. Add. 7. And it agreed that the '864 patent did not claim any of these. "The '864 patent itself," the court wrote, "does not mention Lantus or insulin glargine" and "does not expressly require that the dispenser be pre-filled [with Lantus]" but instead claims only a "'drive mechanism for use in a drug delivery device.'" Add. 10-11.

1. The court concludes the Orange Book regulations are ambiguous. But this did not (in the court's view) make Sanofi's listing of the '864 patent improper. That was so, the court explained, because the Orange Book

[2] The district court granted the purchasers leave to amend their complaint after initially granting Sanofi's motion to dismiss but then dismissed the claims again for the same reasons. *See* Add. 42, Add. 46 (declining to reach a "different conclusion" and "affirm[ing] its prior ruling"). We discuss both rulings (and both motions to dismiss) together.

[3] Sanofi focused its motions to dismiss on the '864 patent because, in its view, prevailing on that patent would mean that "the entire complaint must be dismissed." Add. 3. The district court agreed, and likewise focused its analysis and decision dismissing the Orange-Book-listing claims exclusively on the '864 patent.

listing requirements are "ambiguous" over whether a patent like the '864 patent must claim the finished dosage form of the approved drug product. Add. 46 (concluding it was "not clear whether the 'claims' of the '864 patent" were "sufficient to satisfy" the listing requirements).

The court summarily rejected the purchasers' argument that the statutory and regulatory text expressly required any listed patent to claim the drug, drug substance, or drug product. In support, it cited commentary contained in the FDA's 2003 rule. Add. 21. During that rulemaking, some manufacturers had proposed that patents for "containers that are 'integral' to the drug product" should be listed in the Orange Book. Add. 8. The court concluded that the FDA's final rule left this question "unanswered." Add. 22. By not answering this question, the court held, the FDA had "left a significant ambiguity" over whether "patents directed to drug delivery systems that do not recite the approved active ingredients or formulation should be listed in the Orange Book." Add. 22-23.

To reinforce this conclusion, the court stated that "the issue whether the '864 patent should have been listed is an open question in the industry." Add. 24. In its view, because the FDA had not substantively responded to manufacturers' requests that the FDA allow "patents directed to drug delivery systems that do not recite the approved active ingredients or formulation" to be listed in the Orange

Book, the permissibility of listing such patents "remain[ed] an open question." Add. 23, Add. 24.

2. The court holds that patents "relating to" a drug delivery device may be listed. The court also held that, regardless of whether the '864 patent could independently meet the listing requirements, patents "relating to" a device sold with a drug or drug product are appropriately listed in the Orange Book. Add. 20. After Sanofi invented the injector-pen components claimed by the '864 patent (which could be used with a range of different products), it combined them with Lantus to market Lantus SoloSTAR. JA70. For the court, this meant that the real question "is whether the patents for the Lantus SoloSTAR (including its components) are appropriately listed in the Orange Book." Add. 11.

To answer that question, the court considered whether Lantus SoloSTAR constituted a "pre-filled drug delivery system[]." Add. 46. Because the Orange Book regulations defined "drug product" as including "pre-filled drug delivery systems," the court reasoned that, if Lantus SoloSTAR qualified as a pre-filled drug delivery system, then all patents related to the product—those claiming the drug (insulin glargine) and those claiming the components (the '864 patent and others)—were appropriately listed in the Orange Book "regardless of whether the patent itself expressly references insulin glargine." Add. 46.

The court concluded that Lantus SoloSTAR met the definition of "pre-filled drug delivery system" under the Orange Book regulations. Add. 46. Although Sanofi requested approval of Lantus SoloSTAR as an injectable, the court explained that the FDA generally "has recognized that insulin injector pens constitute 'pre-filled drug delivery systems.'" Add. 46. The court observed that the FDA had approved Lantus SoloSTAR as a "disposable insulin injection device" to be sold "filled with insulin glargine." Add. 46. That led the court to hold that Lantus SoloSTAR "was approved as a drug product" and "a drug delivery system." Add. 44, Add. 45. As a result, it held all patents "relating to" this product were properly listed in the Orange Book. Add. 20. Following this approach would be, in the court's view, "consistent with the purposes of the Orange Book, which is to put others on notice of potentially relevant patents." Add. 20.

3. The court finds Sanofi's decision to list the '864 patent not "objectively baseless." Given the "ambiguous FDA guidance," the court next asked whether it was "unreasonable" for Sanofi to list all of the patents related to Lantus SoloSTAR. Add. 46. As the court saw it, a claim that a defendant "acquired or maintained monopoly power by improper means" can proceed only "if the defendant engaged in unambiguously wrongful conduct that resulted in the improper listing of patents in the Orange Book." Add. 19. But if a defendant "'had a reasonable basis for the submission,' then the listing does not constitute improper

means for antitrust purposes." Add. 19 (quoting *Organon*, 293 F. Supp. 2d at 460). The court held that the relevant inquiry is thus whether the "decision to list" was "unreasonable or objectively baseless." Add. 21. Applying this "objectively baseless" standard, the court concluded that, because Sanofi's decision to list the '864 patent was "reasonable," it "defeats the plaintiffs' antitrust claims." Add. 11.

4. The court dismisses the purchasers' claims. The court then applied this holding to dismiss all of the purchasers' claims. Add. 24 (holding that "the Sherman Act claims, insofar as they rely on the improper Orange Book listing of the '864 patent, are dismissed"). That included not only those claims directly challenging Sanofi's unlawful Orange Book listings as violating the antitrust laws, but also those based on allegations that Sanofi's litigations against Lilly, Merck, and Mylan were shams because "Sanofi sued on the '864 patent knowing that the patent should not have been listed in the Orange Book to begin with," Add. 26 (holding that, because it had "already dismissed the Orange Book listing claim," the purchasers' '864 patent sham litigation claim "need not be addressed further"); Add. 58 (same for the purchasers' serial petitioning claim). So too for the purchasers' allegation that Sanofi engaged in an illegal scheme to prevent and delay any competing versions of insulin glargine products." Add. 61 (dismissing this claim because the purchasers "have not plausibly shown that Sanofi engaged in the improper practice of Orange Book listing and suing competitors to cause

anticompetitive injury"). Ultimately, because all the claims relied on Sanofi's decision to list the pen patents in the Orange Book, the court dismissed the purchasers' complaint in its entirety.

STANDARD OF REVIEW

This Court reviews orders granting motions to dismiss under Rule 12(b)(6) de novo. *Carrero-Ojeda v. Autoridad de Energía Eléctrica*, 755 F.3d 711, 717 (1st Cir. 2014). The Court asks whether the well-pleaded factual allegations, viewed in the light most favorable to the plaintiff, state a claim for which relief can be granted. *See Ocasio-Hernández v. Fortuño-Burset*, 640 F.3d 1, 7 (1st Cir. 2011). A complaint clears this hurdle when the facts alleged and the reasonable inferences they support "plausibly narrate a claim for relief." *Schatz v. Republican State Leadership Comm.*, 669 F.3d 50, 55 (1st Cir. 2012).

SUMMARY OF ARGUMENT

I. This appeal requires nothing more than a straightforward application of the statute and regulations governing Orange Book listings. The statute provides that a manufacturer seeking approval for a drug may list only patents "which claim[] the drug," or "claim[] a method of using such drug." 21 U.S.C. § 355(b)(1). The word "claim" is a patent-law term of art referring to "the portion of the patent document that defines the scope of the patentee's rights." *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996). And the word "drug" means "drug

substance" or "drug product." 21 C.F.R. § 314.53(b)(1). The FDA has defined "drug substance" as the drug's "active ingredient," *id.*, and "drug product" as "a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance." § 314.3. Put simply, Hatch-Waxman's listing requirements restrict Orange Book listings to patents with claims that include the drug's active ingredient or a final dosage form containing the drug's active ingredient.

The '864 patent does not claim any drug substance. Nor does it claim a drug product—a final dosage form containing a drug's active ingredient. The words "Lantus" and "insulin glargine" are nowhere to be found. Instead, the '864 patent claims only a drive mechanism (and several variations) for use in a drug delivery device. According to the patent, this drive mechanism can be used in numerous drug delivery systems, including but not limited to pen-type injectors. The '864 patent thus claims a component that can be used as part of a drug delivery system, but does not claim any completed system—much less a system that contains any particular drug. The applicable statute and regulations therefore provide unambiguously that the '864 patent cannot be listed in the Orange Book.

II. The district court rejected—and largely ignored—this plain-text analysis. It first concluded that the Orange Book listing requirements are ambiguous, relying on the FDA's response to comments during the 2003 rulemaking and a series of later manufacturer petitions. But a review of the FDA's response in 2003 confirms

that it adhered to the statute's plain language. And there is no warrant for departing from the text, or deeming it ambiguous, just because a few manufacturers with strong financial incentives wrote letters to the FDA professing uncertainty about whether they can list patents in the Orange Book whenever those patents somehow "relate[] to" an approved device.

Compounding this error, the district court ruled that the supposed ambiguity of the regulations immunizes Sanofi from antitrust liability. Here, it held that a manufacturer cannot be held liable for improper listings in the Orange Book unless those listings are "unreasonable" or "objectively baseless." It appears as though the court adopted this standard from another district court opinion, which, in turn, misappropriated it from another addressing the exception to *Noerr-Pennington* immunity for sham patent infringement litigation. *See* Add. 19. Invoking that standard here was error. Although Sanofi's decision *was* objectively baseless, the district court's embrace of that high standard misstated the law. There is no reasonableness element for antitrust claims based on a manufacturer's improper listing of a patent that fails to claim the drug.

If the decision below is affirmed, it would allow manufacturers extraordinarily broad latitude to improperly list patents, thus disrupting Hatch-Waxman's delicate balance of incentives. Because these errors infected the district

court's dismissal of all the purchasers' claims in the case, its decision should be reversed.

ARGUMENT

I. Sanofi improperly listed its '864 patent in the Orange Book.

A. Only patents that claim the active ingredient of the drug or a dosage form containing the active ingredient may be listed.

Statutory interpretation "begins with the text." *Plumley v. S. Container, Inc.*, 303 F.3d 364, 369 (1st Cir. 2002). And here, because the text of Hatch-Waxman's requirements is unambiguous, it "ends there as well." *Id.*

The Orange Book's listing criteria are governed by 21 U.S.C. § 355(b)(1). In relevant part, that section provides:

> The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

§ 355(b)(1). The Hatch-Waxman Act thus expressly states that only patents "which claim[] the drug," or "claim[] a method of using such drug," may be listed.[4]

"[C]laim" is "a term of art in patent law." *In re Engage, Inc.*, 544 F.3d 50, 54 (1st Cir. 2008). "It is a cardinal rule of statutory construction that, when Congress employs a term of art, it presumably knows and adopts the cluster of ideas that

[4] Because the statute's reference to patents claiming "a method of using such drug" is not at issue in this case, we do not discuss it.

were attached to each borrowed word in the body of learning from which it is taken." *Air Wis. Airlines Corp. v. Hoeper*, 571 U.S. 237, 248 (2014) (citation omitted). Section 355(b)(1)'s reference to patents that "claim the drug" must therefore be read in accordance with the meaning of "claim" in patent law. *See Markman*, 517 U.S. at 374 ("[T]he word 'claim' is used . . . in [a] sense peculiar to patent law.").

Put simply, a "patent claim" is "the portion of the patent document that defines the scope of the patentee's rights." *Id.* at 372. "Patent claims are specific, formal language recited at the conclusion of a patent 'specification,' which is the required written description of an invention (and is accompanied by drawings or figures) in a patent or patent application." Edward D. Manzo, *Patent Claim Construction in the Federal Circuit* § 1:1 (2018 ed.). A claim "covers and secures a process, a machine, a manufacture, a composition of matter, or a design," *Markman*, 517 U.S. at 373, and it is "a 'bedrock principle' of patent law that 'the claims of a patent define the invention to which the patentee is entitled the right to exclude,'" *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc) (citation omitted).

As with "claim," the term "drug" in section 355(b)(1) also holds a clear meaning. The FDA's implementing regulations define "drug" to include (1) a "drug substance," which is a drug's "active ingredient," or (2) a "drug product," which is "a finished dosage form, e.g., tablet, capsule, or solution, that contains a

drug substance." *See* 21 C.F.R. § 314.53(b)(1) (cross-referencing § 314.3). Because both of these definitions, at bottom, require the drug's active ingredient, to claim the "drug" a patent must claim the drug's active ingredient or a finished dosage form containing the drug's active ingredient. And, as the FDA has made clear, patents that "are distinct from the drug product"—like those "claiming packaging"—do not "meet[] the statutory requirements" and "must not be submitted." 68 Fed. Reg. at 36680, 36683; § 314.53(b)(1).

Applying this settled understanding resolves the meaning of section 355(b)(1). Only patents that "cover and secure" the approved drug's active ingredient or a dosage form containing the active ingredient may be listed in the Orange Book.

B. The '864 patent does not claim the active ingredient of a drug or a final dosage form containing an active ingredient.

This appeal concerns Sanofi's patents over its SoloSTAR invention—a universal, non-drug-specific injector pen designed for use across a range of drug products. Chief among these patents is the '864 patent. As the district court acknowledged, "the '864 patent itself does not mention Lantus or insulin glargine." Add. 10. Nor does the '864 patent claim a pre-filled drug delivery system, or make any reference to a device pre-filled with any particular drug. The patent does not even specify that the claimed invention must be used solely in combination with drugs administered with pen-type injectors. Instead, as explained in the "Technical Field," the patent claims only a series of "drive mechanisms suitable for use in drug

delivery devices, in particular pen-type injectors, having dosage setting means, enabling the administration of medicinal products from a multi-dose cartridge." Add. 85.

There is no plausible interpretation of section 355(b)(1) or its implementing regulations under which the '864 patent should be listed in the Orange Book. That is because there is no plausible interpretation of the '864 patent under which it "claims" a drug's active ingredient or the finished dosage form containing that active ingredient. § 355(b)(1); § 314.53(b)(1). The patent claims a series of drive mechanisms with no reference whatsoever to those mechanisms containing any active ingredient. Nor does it describe a drug delivery device incorporating those mechanisms being pre-filled with any active ingredient. The words "Lantus," "insulin glargine," and "insulin" do not appear anywhere in the patent's "claim."[5]

Any doubt on this score is resolved by a comparison of the "claim" sections of Sanofi's patent claiming insulin glargine (the '722 patent, **Figure 1**) with its patent claiming the drive mechanism (the '864 patent, **Figure 2**). The '722 patent claims "an insulin derivative" (claims 1-5, 10-11, 15), "a pharmaceutical composition" (claims 6-8, 12-14), and "a method for treating a patient suffering from diabetes mellitius, which comprises administering to said patient a

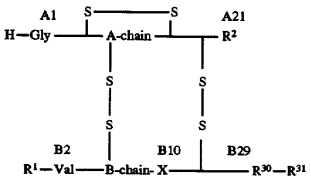
[5] The word "insulin" appears once in the '864 patent—in the background section, where it is listed as one of several examples of the drug products that the claimed "drug delivery device" might dispense. Add. 85.

pharmaceutical composition" (claim 9). This is what it looks like when a patent claims a drug.

Figure 1: Claims in the '722 Patent

I claim:

1. An insulin derivative having an isoelectric point between 5 and 8.5, or a physiologically tolerated salt thereof, of the Formula II
in which:



R^1 at position B1 denotes H or H-Phe;

R^2 at position A21 denotes a genetically encodable L-amino acid selected from the group consisting of Gly, Ala, Val,

Leu, Ile, Pro, Phe, Trp, Met, Ser, Thr, Cys, Tyr, Asp, and Glu;

R^{30} represents the residue of a neutral genetically encodable L-amino acid selected from the group consisting of Ala, Thr, and Ser;

R^{31} represents 1, 2, or 3 neutral or basic α-amino acids, wherein at least one of the α-amino acids is selected from the group consisting of Arg, Lys, Hyl, Orn, Cit, and His;

X represents His at position B10; and the sequences A1 to A20 and B1 to B29 in Formula II correspond to a mammalian insulin;

excluding those insulin derivatives in which simultaneously:

R^1 at position B1 denotes Phe; and

R^{31} is one alpha amino acid having a terminal carboxyl group.

2. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein R^1 in formula II represents H-Phe.

3. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein R^2 in formula II represents Gly, Ala, Ser, Thr, Asp, or Glu.

4. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein R^{31} in formula II represents Arg-Arg-OH.

5. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein the sequences (A1 to A20) and (B1 to B29) in formula II are the sequences of human, porcine, or bovine insulin.

6. A pharmaceutical composition that contains an effective amount of at least one insulin derivative of the formula II, or at least one of the physiologically tolerated salts thereof, as claimed in claim **1**, in dissolved, amorphous or crystalline form for the treatment of diabetes.

7. A pharmaceutical composition as claimed in claim **6**, which additionally contains 1 µg to 2 mg of zinc/ml.

8. A pharmaceutical composition as claimed in claim **6**, which additionally contains unmodified insulin.

9. A method for treating a patient suffering from diabetes mellitus, which comprises administering to said patient a pharmaceutical composition as claimed in claim **6**.

10. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **3**, wherein R^2 in formula II represents Asp.

11. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **5**, wherein the sequences (A1 to A20) and (B1 to B29) in formula II are the sequences of human insulin.

12. A pharmaceutical composition that contains an effective amount of at least one insulin derivative of the formula II, or at least one of the physiologically tolerated salts thereof, as claimed in claim **8**, in dissolved form for the treatment of diabetes.

13. A pharmaceutical composition as claimed in claim **7**, which additionally contains 5 µg to 200 µg of zinc/ml.

14. A pharmaceutical composition as claimed in claim **8**, wherein said unmodified insulin is unmodified human insulin.

15. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **5**, wherein R^1 represents H-Phe, R^2 represents Gly, R^{30} represents Thr, and R^{31} represents Arg-Arg-OH.

* * * * *

In contrast, none of the '864 patent's ten claims refer to any active ingredient or any dosage form containing any active ingredient. Instead, the patent claims, in

general terms unconnected to any drug, "a drive mechanism for use in a drug delivery device" (claims 1-2, 8) and a series of variations on the "drive mechanism[s]" (claims 3-7, 9-10).

Figure 2: Claims in the '864 Patent

The invention claimed is:

1. A drive mechanism for use in a drug delivery device comprising:

a housing having a helical thread;

a dose dial sleeve having a helical thread engaged with the helical thread of the housing;

a drive sleeve having two radially extending flanges spaced a distance apart and having an outer helical thread there between, where the drive sleeve is releasably connected to the dose dial sleeve;

a piston rod threadedly engaged with the drive sleeve; and

a clutch mechanism located between the dose dial sleeve and the drive sleeve.

2. A drive mechanism for use in a drug delivery device is provided comprising:

a housing having a helical thread along an inner surface,

a dose dial sleeve having a helical thread on an outer surface engaged with the helical thread of the housing;

a drive sleeve releasably connected to the dose dial sleeve; and

a clutch mechanism located between the dose dial sleeve and the drive sleeve;

wherein the clutch mechanism is configured such that,

a) when the dose dial sleeve and the drive sleeve are coupled, both are allowed to rotate with respect to the housing; and

b) when the dose dial sleeve and the drive sleeve are de-coupled, rotation of the dose dial sleeve with respect to the housing is allowed, while rotation of the drive sleeve with respect to the housing is prevented, whereby axial movement of the drive sleeve is allowed so that a force is transferred in a longitudinal direction to a proximal end of the drug delivery device.

3. The drive mechanism of claim **2** further comprising a piston rod having a first external thread and a second external thread, where the first external thread is threadedly engaged with an insert, and where the second external thread is threadedly engaged with an internal thread on the drive sleeve.

4. The drive mechanism of claim **2** where the drive sleeve has two radially extending flanges spaced a distance apart and having an outer helical thread there between and where the drive sleeve is releasably connected to the dose dial sleeve.

5. The drive mechanism of claim **4** further comprising a dose limiting mechanism.

6. The drive mechanism of claim **5** wherein said dose limiting mechanism is disposed between said first radially extending flange and said second radially extending flange.

7. The drive mechanism of claim **6** wherein said dose limiting mechanism comprises a nut threadedly engaged with the outer helical thread of the drive sleeve and is splined to an internal surface of the housing to prevent the nut from rotating while allowing relative longitudinal movement between the two radially extending flanges, whereby the longitudinal movement is proportional to dispensed doses.

8. A drive mechanism for use in a drug delivery device comprising:

a) a main housing having a first end and a second end, a helical thread having a first lead, an insert rotationally fixed to the housing having a thread with a second lead;

b) a dose dial sleeve having a helical thread engaged with the helical thread of the main housing configured so that during dose selection the dose dial sleeve rotates and extends axially from the second end of the main housing and during dose delivery rotates and moves axially back into the main housing;

c) a tubular drive sleeve having an internal surface and an outer surface having disposed thereon an intermediate thread, where the tubular drive sleeve is releasably connected to the dose dial sleeve through a clutch located between the dose dial sleeve and the tubular drive sleeve and where the tubular drive sleeve has an internal helical thread having a lead equal to the first lead;

d) a piston rod having a first external thread and a second external thread, where the first external thread has a lead equal to the second lead that is different and of opposite disposition than the first lead and is threadedly engaged with the insert, and where the second external thread is threadedly engaged with the internal thread of the tubular drive sleeve;

wherein,

when the dose dial sleeve and the tubular drive sleeve are coupled during dose section, both are allowed to rotate with respect to both the main housing and the piston rod; and

when the dose dial sleeve and the tubular drive sleeve are de-coupled during dose delivery, rotation of the dose dial sleeve with respect to the main housing is allowed, while rotation of the tubular drive sleeve with respect to the main housing is prevented, whereby axial movement of the tubular drive sleeve is allowed causing the piston rod to rotate through the tread of the insert and moving axially through the insert so that a force is transferred from the piston rod to a cartridge piston.

9. The drive mechanism of claim **8** wherein the intermediate thread is disposed between two radially extending flanges on the outer surface of the tubular drive sleeve.

10. The drive mechanism of claim **8** wherein the opposite disposition of the second lead of the first external thread compared to the first lead prevents the piston rod from moving during dose selection.

* * * * *

Suffice to say: a patent does not claim a drug or a dosage form of a drug when it makes no mention of that drug. It is thus unambiguous that the '864 patent cannot be listed in the Orange Book.

II. The district court erred in concluding that Sanofi could escape liability for its improper Orange Book listing.

The district court rejected this plain-text analysis. It first found the Orange Book listing requirements ambiguous as to whether manufacturers may list patents "relating to" a device, even if the "patent itself does not mention" the drug. The court reasoned that Sanofi could not be held liable if its "conduct" in listing the patent was "reasonable" and not "objectively baseless." Add. 43, Add. 21. Both of these conclusions are wrong. The Orange Book listing requirements are not ambiguous and antitrust liability is not limited only "objectively baseless" listings.

A. The Orange Book listing requirements are not ambiguous.

The district court held that section 355(b)(1) and the FDA's regulations leave open the question whether the '864 patent could be listed in the Orange Book. The court gave two reasons: first, the FDA did not answer certain industry comments, which "left a significant ambiguity" over whether "patents directed to drug delivery systems that do not recite the approved active ingredients or formulation should be listed in the Orange Book," Add. 22-23; and, second, it is reasonable to believe that patents "relating to" a pre-filled drug delivery system must be listed, Add. 20. This

logic is wrong on its own terms and offers no basis for departing from the statute's text.

1. The FDA's response to comments and petitions did not introduce ambiguity into the Orange Book requirements.

The district court based much of its decision on an analysis of the FDA's response to comments during the 2003 rulemaking and the agency's response to post-2003 manufacturer petitions. Its reasoning on both points was mistaken.

As explained above, the FDA revised its Orange Book listing regulations in 2003. *See supra* at 12-14. One question it considered was whether patents claiming "containers and delivery systems" claim "packaging" and so cannot be listed in the Orange Book. 68 Fed. Reg. at 36680. "Some comments," the FDA noted, "stated that patents claiming devices or containers that are 'integral' to the drug product or require prior FDA approval should be submitted and listed. These comments distinguished between packaging and devices such as metered dose inhalers and transdermal patches, which are drug delivery systems used and approved in combination with a drug." *Id.* The FDA responded:

> We agree that patents claiming a package or container must not be submitted. Such packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission. However, we have clarified the rule to ensure that if the patent claims the drug product as defined in § 314.3, the patent must be submitted for listing.

> Section 314.3 defines a "drug product" as ". . . a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." The appendix in the Orange Book lists current dosage forms for approved drug products. The list includes metered aerosols, capsules, metered sprays, gels, and pre-filled drug delivery systems. The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product. Patents must not be submitted for bottles or containers and other packaging, as these are not "dosage forms . . . ."

Id.

The district court recognized that it must defer to the FDA's interpretation of its own regulations, but concluded that "the Response itself is ambiguous, and does not directly address the comments, which concerned all delivery devices that are 'integral' to the drug product or require prior FDA approval." Add. 21.

The Response was not ambiguous. The comments asked whether patents claiming only containers and packaging should be listed in the Orange Book. In *direct* response, and consistent with section 355(b)(1), the FDA stated that "patents claiming a package or container *must not be submitted*," since they "are distinct from the drug product and thus fall outside of the requirements for patent submission." 68 Fed. Reg. at 36680 (emphasis added). It confirmed that where a patent does claim a drug product—defined as "a finished dosage form, e.g., tablet capsule, or solution, that *contains* a drug substance," § 314.3 (emphasis added)—it may be listed in the Orange Book. True, the FDA did not remark upon the comments' proposed

"integral to" test. It did not need to. Its response unequivocally explained which patents claiming containers and packaging may and may not be listed in the Orange Book. The distinction does not depend on whether the invention claimed in a patent is "integral" (or otherwise "related to") to an approved drug product.

In language squarely applicable here, the FDA emphasized that "the key factor is whether" the submitted patent "*claims the finished dosage form of the approved drug product*." 68 Fed. Reg. at 36680 (emphasis added). Of course, a patent could claim a "pre-filled drug delivery system[]" that "'contains a drug substance . . . in association with one or more other ingredients.'" *Id.* (quoting § 314.3). But a patent that does not claim a "pre-filled drug delivery system," and claims only "containers and other packaging" that might someday be used with one or more drugs, cannot be listed in the Orange Book. *Id.* That is because a patent that claims "containers and other packaging" alone does not claim a "dosage form." *Id.* The FDA's response to comments in the 2003 rulemaking process thus bears directly on this case and unambiguously precludes listing the '864 patent in the Orange Book.

Since 2003, the FDA received several manufacturer petitions seeking to broaden the listing criteria. *See supra* at 14-15. These petitions profess uncertainty about the meaning of the 2003 rule and make policy arguments in favor of allowing manufacturers to list a broader range of patents in the Orange Book. Several manufacturers stated their intent to list patents "that claim all or a portion

of integrated drug-device products, regardless of whether the approved drug substance is specifically mentioned in the claims of such patents." JA884. In one manufacturer's opinion, "Orange Book listing is required for patents directed to [pre-filled] drug delivery systems even if the patents disclose but do not claim, or neither disclose nor claim, the active ingredient or formulation of the approved drug product." JA882. On this view, when a claimed invention is neither a drug nor a dosage form containing a drug, but the invention is marketed as part of a dosage form containing a drug, that patent is properly listed in the Orange Book.

The FDA has declined to respond substantively to these petitions. Instead, the FDA has noted that, "given the numerous demands on the Agency's resources" and "the need to address other Agency priorities," it has "not yet resolved the issues raised" by the requests and has been "unable to reach a decision." *See, e.g.*, JA895.

The district court treated the petitions, and the FDA's response, as evidence that the Orange Book listing regulations' meaning "remains an open question." Add. 24. That is incorrect. To start, taken both together and in isolation, the statute, its implementing regulations, and the FDA's rulemaking statements are all unambiguous. It is not surprising that manufacturers with strong financial and competitive incentives persist in seeking to inject ambiguity that would allow them to prolong their market monopolies. But none of their petitions, which are heavy

on policy and light on law, offer a plausible explanation of why the relevant provisions are properly read to support their view. And this request by a few industry insiders offers no warrant for giving the statutory and regulatory terms anything other than their plain meaning—which, as described above, limits Orange Book listings to patents claiming the active ingredient or a finished dosage form that contains it. This Court's approach to statutory interpretation is, and always has been, straightforward: "In the absence of ambiguity," it does "not look beyond the plain meaning of the statutory language." *Herman v. Hector I. Nieves Transp., Inc.*, 244 F.3d 32, 34 (1st Cir. 2001) (citations omitted).

Nor can the FDA's interim response be understood as either endorsing the petitions' merits or their claims of regulatory ambiguity. These responses are standard practice at the FDA. *See In re Wellbutrin XL Antitrust Litig.*, No. 08-CV-2431, 2012 WL 1657734, at *29 (E.D. Pa. May 11, 2012) ("Such interim FDA responses are typically boilerplate answers issued before the FDA has even reviewed and considered the petition."). When the FDA issues a response of the kind it issued here, "the FDA has not enacted or rescinded any rule, but has rather simply written a letter indicating that it has not reached a decision and offering an explanation, however brief, of why that is so." *Hill Dermaceuticals, Inc. v. U.S. Food & Drug Admin.*, 524 F. Supp. 2d 5, 10 (D.D.C. 2007). That step is required by regulations instructing the FDA Commissioner to respond to petitions "within 180

days of receipt of the petition." 21 C.F.R. § 10.30(e)(2); *see also* § 10.30(e)(1) (allowing the FDA to account for "available agency resources" and "the priority assigned to the petition considering both the category of subject matter involved and the overall work of the agency"). But it goes no further.

The FDA's response did not admit or acknowledge some ambiguity; the agency simply did not address or express a view on the matters raised by the petitions.

2. The district court's "relating to" standard contravenes the plain text of the statute and regulations.

Relying, in part, on its mistaken understanding of the FDA's rulemaking commentary, the district court held that patents "relating to" a device sold with a drug or drug product may be listed in the Orange Book. The court assigned determinative weight to the fact that "Lantus SoloSTAR is sold loaded with a dosage of insulin glargine," and "the FDA approval obviously contemplated a pre-filled device." Add. 10. Because the Orange Book's list of dosage forms includes "pre-filled drug delivery systems," the court deemed it "not unreasonable for Sanofi to believe that it should list Lantus SoloSTAR, *and its components*, in the Orange Book." Add. 20 (emphasis added).

This reasoning incorrectly places the FDA-approved *product* at the center of the Orange Book listing inquiry: under this approach, if the FDA has approved a product that qualifies as a "drug product" under § 314.3, then any patent claiming

any component of that product may be listed in the Orange Book. Under this theory, *if* Lantus SoloSTAR qualifies as a drug product because it is pre-filled with insulin glargine, *then* the patents for every component of it may be listed, even if none (or few) would otherwise qualify for listing.

As a policy matter, there may be arguments for and against this product-centered approach to Orange Book listing. The district court implied sympathy for Sanofi's policy position, noting that the company and its competitors would benefit from knowing whether the competitor "products"—which "included both a drug and a drug delivery system"—"were subject to patent infringement claims." Add. 20. Of course, ensuring such notice may be a legitimate policy goal. But so are promoting free competition, facilitating competitor entry, and respecting the limits of patent law. *See, e.g.*, 68 Fed. Reg. at 36676. Those goals—all embodied in Hatch-Waxman—would be substantially undermined if manufacturers like Sanofi could artificially extend their monopolies by listing non-drug-specific patents in the Orange Book, precluding competition.

Regardless of who is right on that policy question, though, the plain text of Hatch-Waxman resolves it as a legal matter. Section 355(b)(1) provides that "the applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug." The clear restriction is

unavoidable: only a patent "which claims the drug . . . or which claims a method of using such drug" may be submitted. § 355(b)(1). Nothing in this text hints that a patent which does *not* claim the drug or a method of using such drug, but instead claims a general invention that is subsequently incorporated into an FDA-approved product, may be listed.[6]

Adopting the reasoning of the district court would require this Court to rewrite the statute as follows:

> [T]he applicant shall file with the application the patent number and the expiration date of any patent **relating to** ~~which claims~~ the drug for which the applicant submitted the application or which **relates to** ~~claims~~ a method of using such drug . . .

But this Court is "not at liberty to rewrite the statute." *Henry Schein, Inc. v. Archer & White Sales, Inc.*, 139 S. Ct. 524, 528 (2019). Nor may it rewrite the FDA's regulations, which, consistent with the unambiguous statutory text, limit Orange Book listings to patents that "claim" the active ingredient or a finished dosage form *containing* the active ingredient. *See* § 314.53(b)(1); § 314.3.

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[6] For this reason, the district court's belief that the "record compels the conclusion" that Lantus SoloSTAR was approved not "only as packaging" but "as a drug delivery system," although wrong, is irrelevant. Add. 45. Even if the commercially available Lantus SoloSTAR *is* a "drug delivery system" (and there is no way to square this with Sanofi's sNDA for the SoloSTAR, which proposed changing the packaging for insulin glargine but *not* the dosage form), it is undisputed that the '864 patent does not claim this product.

Bottom line: As a matter of law, the question is whether the *patent* claims the drug or a method of using the drug, not whether the *product* sold to the public relates to an otherwise-excluded patent. The district court erred in treating this question as "open" and "ambiguous," and its decision therefore must be reversed.

B. Antitrust liability for improperly listing a patent in the Orange Book does not turn on whether the listing was "unreasonable or objectively baseless."

The district court compounded its mistaken interpretation of Hatch-Waxman's Orange Book listing requirements with a second legal error. After acknowledging that an improper Orange Book listing can "subject the patent holder to antitrust liability," it held that antitrust liability also requires proof that the listing was "unreasonable." Add. 42. This standard, which immunizes manufacturers unless their Orange Book listings are "objectively baseless," Add. 21, has no legal foundation and would do violence to the scheme of private enforcement required by Hatch-Waxman.

To succeed on a claim under section 2 of the Sherman Act, a plaintiff must demonstrate two elements: "(1) that the defendant possesses monopoly power in the relevant market, and (2) that the defendant has acquired or maintained that power by improper means," i.e., "exclusionary conduct." *Town of Concord v. Boston Edison Co.*, 915 F.2d 17, 21 (1st Cir. 1990). It is the second element that matters here: unlawfully maintaining monopoly power by leveraging a patent to manipulate the

competitor-drug-application process can qualify as exclusionary conduct. *See* Add. 19; *In re Lipitor Antitrust Litig.*, 868 F.3d 231, 271-72 (3d Cir. 2017). Drawing on "a century of case law on monopolization," to be "condemned as exclusionary, a monopolist's conduct must have anti-competitive *effect*." *United States v. Microsoft Corp.*, 253 F.3d 34, 58 (D.C. Cir. 2001) (emphasis added). The "focus," in other words, is "upon the effect of th[e] conduct, *not upon the intent behind it*." *Id.* at 59 (emphasis added).

The district court offered no persuasive justification for departing from the settled rule. It suggested that an earlier case, *Organon Inc. v. Mylan Pharmaceuticals, Inc.*, supported its decision to impose a reasonableness requirement on the purchasers' claims. Add. 43 (citing *Organon*, 293 F. Supp. 2d at 460). But while *Organon* appeared to embrace this standard, it contains no reasoning of its own. Instead, it cited another case—*In re Buspirone Patent Litigation*, 185 F. Supp. 2d 363 (S.D.N.Y. 2002)—simply asserting that antitrust liability cannot exist where there is "a reasonable basis for the submission." *Organon*, 293 F. Supp. 2d at 60.

Reliance on *Buspirone* here, though, is a category error. Much like this case, *Buspirone* involved claims that a manufacturer anticompetitively delayed competitors by improperly listing patents in the Orange Book and then suing to halt FDA approval of the competitors. But unlike in this case, the manufacturer in *Buspirone* relied principally on the *Noerr-Pennington* doctrine as a defense. *See*

Buspirone, 185 F. Supp. 2d at 369. As Judge Koeltl noted, a patent holder can lose *Noerr-Pennington* immunity "if the patent infringement suit was a mere sham." *Id.* The "mere sham" standard is met when the suit "was objectively baseless and subjectively motivated by a desire to impose collateral, anti-competitive injury." *Id.* It was *only* in the context of evaluating this question—whether the manufacturer could rely on *Noerr-Pennington*—that Judge Koeltl held the manufacturer's "conduct in listing the [disputed] Patent and bringing the subsequent patent infringement suits was objectively baseless." *Id.* at 376. As Judge Koeltl made clear, however, the *Noerr-Pennington* doctrine does not apply to Orange Book listing claims. *Id.* (noting that, even if it did, the brand company's actions were objectively baseless).

The "objectively baseless" standard from *Buspirone* has no proper application outside the *Noerr-Pennington* context. *See Litton Sys., Inc. v. AT&T Co.*, 700 F.2d 785, 807 (2d Cir. 1983) (refusing to extend *Noerr-Pennington* where there is no "repugnancy between the antitrust and regulatory provisions"). By citing and quoting this standard from *Buspirone*—and by relying on *Organon* (which merely cites, without discussion, to *Buspirone*)—the district court erred. The question here is whether Sanofi improperly listed the '864 patent, and, in turn, unlawfully prolonged its insulin glargine monopoly, not whether its decision to do so was "unreasonable" or "objectively baseless."

That understanding is supported by the text of section 355(b)(1), which provides two independent criteria for listing a patent in the Orange Book.

> The applicant shall file with the application the patent number and the expiration date of any patent
>
> (1) which claims the drug for which the applicant submitted the application or which claims a method of using such drug
>
> *and*
>
> (2) with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.

§ 355(b)(1) (formatting and emphasis added). The first criterion does not include any reasonableness requirement: applicants *shall* list patents that meet the stated criteria (and, by negative implication, *shall not* list patents that do not). The second criterion, in contrast, expressly provides for a reasonableness inquiry: patents that satisfy the first criterion may be listed only if they could "reasonably" be asserted in an infringement suit.

That is a distinction with a difference. When "'Congress includes particular language in one section of a statute but omits it in another'—let alone in the very next provision—this Court 'presume[s]' that Congress intended a difference in meaning." *Loughrin v. United States*, 573 U.S. 351, 358 (2014) (quoting *Russello v. United States*, 464 U.S. 16, 23 (1983)). Since the criteria appear next to each other in a single provision and operate conjunctively—each must be satisfied in order to

comply with section 355(b)(1)—importing the reasonableness requirement from the second requirement into the first would "render[] what Congress has plainly done . . . devoid of reason and effect." *Great-West Life & Annuity Ins. Co. v. Knudson*, 534 U.S. 204, 217–18 (2002); *see RadLAX Gateway Hotel, LLC v. Amalgamated Bank*, 566 U.S. 639, 645 (2012) ("[I]f possible, effect shall be given to every clause and part of a statute." (citation omitted)). The district court erred in rewriting the first criterion to impose a requirement that Congress decided against including.

And make no mistake: The district court's error risks undermining Hatch-Waxman's balance between expediting non-infringing competition and incentivizing innovation. The FDA has made clear that it will not police Orange Book listings. *See* 68 Fed. Reg. at 36683 (FDA describing its own "patent listing role" as "ministerial"); *Am. Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001) ("[T]he FDA administers the Hatch-Waxman Amendments in a ministerial fashion simply following the intent of the parties that list patents."). And it has recognized that "an applicant's potential liability" "will help ensure that accurate patent information is submitted." 59 Fed. Reg. at 50344; *see also* 68 Fed. Reg. at 36683 (noting that it is a "fundamental assumption of the Hatch-Waxman Amendments" that "the courts are the appropriate mechanism" for resolving these disputes).

Without antitrust liability as a guardrail against improper listings, and as a force pushing toward compliance with section 355(b)(1), manufacturers might take an overly generous view of their prerogative to list patents. Given the powerful and anticompetitive legal consequences triggered by a listing, some manufacturers might be tempted to abandon the law, even when the patents at issue are not the kind Congress intended to protect. *See Buspirone*, 185 F. Supp. 2d at 373. But the public has "a paramount interest in seeing that patent monopolies spring from backgrounds free from fraud or other inequitable conduct and that such monopolies are kept within their legitimate scope." *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 816 (1945). Immunizing this conduct would have "far-reaching social and economic consequences." *Id.*

This case exemplifies that risk. If the district court's forgiving standard of review is accepted, and manufacturers can evade antitrust liability by divining any statutory or regulatory ambiguity, the incentives for adherence to the listing criteria will be dangerously undermined. Ordinary principles of antitrust liability—which prohibit the creation or maintenance of a monopoly through improper means—should have led the court to deny the motion to dismiss here. When section 355(b)(1) does not provide for listing a patent, listing that patent anyway is an "improper means" of acquiring market power. No rule of antitrust law, and

nothing in the text of section 355(b)(1), justifies the district court's contrary conclusion.

CONCLUSION

For these reasons, the Court should reverse the district court's dismissal of the purchasers' claims.

Respectfully submitted,

/s/ Matthew W.H. Wessler
MATTHEW W.H. WESSLER
JOSHUA MATZ
GUPTA WESSLER PLLC
1900 L Street, NW
Washington, DC 20036
(202) 888-1741
matt@guptawessler.com

THOMAS M. SOBOL
KRISTIE A. LASALLE
KRISTEN A. JOHNSON
HAGENS BERMAN SOBOL SHAPIRO LLP
55 Cambridge Parkway, Suite 301
Cambridge, MA 02142
(617) 482-3700
tom@hbsslaw.com

JOHN D. RADICE
RADICE LAW FIRM, P.C.
34 Sunset Blvd
Long Beach, NJ 08008
(646) 245-8502

JOSEPH M. VANEK
DAVID P. GERMAINE
JOHN P. BJORK
VANEK, VICKERS & MASINI, P.C.
55 W. Monroe, Suite 3500
Chicago, IL 60603
(312) 224-1500

PAUL E. SLATER
MATTHEW T. SLATER
SPERLING & SLATER, P.C.
55 W. Monroe, Suite 3200
Chicago, IL 60603
(312) 641-3200

LINDA P. NUSSBAUM
BRADLEY J. DEMUTH
NUSSBAUM LAW GROUP, P.C.
1211 Avenue of the Americas, 40th Floor
New York, NY 10036
(917) 438-9189

JUAN R. RIVERA FONT
JUAN R. RIVERA FONT LLC
Ave. González Giusti #27, Suite 602
Guaynabo, PR 00968
(787) 751-5290

March 15, 2019

Counsel for Appellants

CERTIFICATE OF COMPLIANCE

This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B) because this brief contains 11,972 words excluding the parts of the brief exempted by Rule 32(f). This brief complies with the typeface requirements of Rule 32(a)(5) and the type-style requirements of Rule 32(a)(6) because this brief has been prepared in proportionally spaced typeface using Microsoft Word in 14 point Baskerville font.

/s/ Matthew W.H. Wessler
Matthew W.H. Wessler
Counsel for Appellants

March 15, 2019

CERTIFICATE OF SERVICE

I hereby certify that on March 15, 2019, I electronically filed the foregoing brief with the Clerk of the Court for the U.S. Court of Appeals for the First Circuit by using the CM/ECF system. All participants are registered CM/ECF users, and will be served by the appellate CM/ECF system:

JULIE E. MCEVOY
jmcevoy@jonesday.com
ROSANNA K. MCCALIPS
rkmccalips@jonesday.com
ALISHA M. CROVETTO
acrovetto@jonesday.com
JONES DAY
51 Louisiana Ave NW
Washington, DC 20001
(202) 879-3939

LAURA DISS GRADEL
lgradel@jonesday.com
JONES DAY
100 High Street, 21st Floor
Boston, MA 02110
(617) 960-3939

/s/ Matthew W.H. Wessler
Matthew W.H. Wessler
Counsel for Appellants

ADDENDUM

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UNITED STATES DISTRICT COURT FOR
THE DISTRICT OF MASSACHUSETTS

In re LANTUS DIRECT PURCHASER ANTITRUST LITIGATION	CIVIL ACTION NO. 16-12652-JGD

MEMORANDUM OF DECISION AND ORDER ON DEFENDANT'S MOTION TO DISMISS

January 10, 2018

DEIN, U.S.M.J.

I. INTRODUCTION

Plaintiffs, FWK Holdings, LLC and Cesar Castillo, Inc., are purchasers of the insulin glargine products Lantus and Lantus SoloSTAR, which are used in the treatment of Type I and Type II diabetes. They have brought a purported class action on behalf of themselves and all others similarly situated against Sanofi-Aventis U.S. LLC ("Sanofi"), the manufacturer of both products, alleging that Sanofi improperly delayed the entry into the market of a competitive product manufactured by Eli Lilly and Company ("Lilly"). In their Amended Class Action Complaint, plaintiffs assert two claims under Section 2 of the Sherman Act (15 U.S.C. § 2) — one for monopolization and one for attempted monopolization. It is the plaintiffs' contention that Sanofi prolonged its monopoly for insulin glargine by (1) improperly listing six patents in the U.S. Federal Drug Administration's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") and (2) pursuing sham litigation against Lilly in which Sanofi asserted claims of patent infringement, allegedly without any basis. The litigation was settled by Sanofi and Lilly shortly before trial.

This matter is before the court on "Defendant Sanofi-Aventis U.S. LLC's Motion to Dismiss Pursuant to Fed. R. Civ. P. 12(b)(6)" (Docket No. 21). Sanofi argues that the court should dismiss both counts of the Amended Complaint (Docket No. 10) ("Am. Compl.") pursuant to Federal Rule of Civil Procedure 12(b)(6) for failure to state a claim upon which relief can be granted. This court finds that the plaintiffs have failed to allege sufficient facts to support a finding of antitrust liability against Sanofi for listing patents in the Orange Book unreasonably, or for engaging in sham litigation with Lilly. Therefore, and for the reasons detailed herein, Sanofi's Motion is ALLOWED and the Amended Complaint is dismissed without prejudice.

II. STATEMENT OF FACTS

Overview

Sanofi is a life sciences company that sells, among other medicines, Lantus — an insulin glargine solution used for Type I and Type II diabetes. Am. Compl. ¶ 3; Def. Mem. (Docket No. 22) at 1. Lantus is sold in vial form or in an injector pen formulation known as Lantus SoloSTAR. Am. Compl. ¶ 3. Sanofi gained approval from the FDA to sell Lantus in vial form in 2000 and to sell Lantus SoloSTAR in 2007. Id. ¶¶ 3, 127. According to the plaintiffs, the original patent for insulin glargine, U.S. Patent No. 5,656,722 ("the '722 patent"), as extended by a period of pediatric exclusivity,[1] expired on February 12, 2015. Id. ¶¶ 103, 105. The plaintiffs contend that "[t]his lawsuit does not challenge Sanofi's right to charge supra-competitive prices for Lantus products up until February of 2015. But it does challenge Sanofi's unlawful conduct in

[1] Pediatric exclusivity grants "an additional six months of market exclusivity to innovator companies that, at written request of the FDA, submit pediatric studies on particular drugs." Nadja R. Allen, *When Does the Clock Begin Ticking?*, 30 AIPLA Q.J. 1, 10-11 (2002).

prolonging its exclusive position beyond February of 2015, i.e., beyond the expiration of the '722 patent." Id. ¶ 121.

Relevant to this litigation, Sanofi is also the holder of other "formulation" patents covering preparations of insulin,[2] and "pen" patents covering injector pens or components thereof.[3] Id. ¶¶ 131-32, 161-66, 221. Sanofi listed these patents in the FDA's Orange Book which, as described below, is intended to put other drug manufacturers on notice of relevant patents, and can trigger a patent-holder's right to bar the entry of a competitor's product into the market while patent infringement claims are resolved. See, e.g., id. ¶ 296. While the plaintiffs contend that Sanofi's listing of six of these patents in the Orange Book was wrongful, and were part of a scheme "to maintain and extend its monopoly power with respect to insulin glargine products – sold under the brand names Lantus and Lantus SoloSTAR," id. ¶ 297, Sanofi has focused its motion to dismiss on one of the "pen" patents, the '864 patent. If Sanofi prevails with respect to its treatment of the '864 patent, the entire complaint must be dismissed as the plaintiffs would not be able to establish any damages in connection with any of the other patents. For all the reasons detailed herein, this court concludes that the plaintiffs have failed to sufficiently allege a claim that the '864 patent was improperly listed in the Orange Book.

[2] These are U.S. Patent No. 7,476,652 ("the '652 patent"), and U.S. Patent No. 7,713,930 ("the '930 patent").

[3] These are U.S. Patent No. 7,918,833 ("the '833 patent"), U.S. Patent No. 8,512,297 ("the '297 patent"), U.S Patent No. 8,556,864 ("the '864 patent"), U.S. Patent No. 8,603,044 ("the '044 patent"), and U.S. Patent No. 8,679,069 ("the '069 patent").

In 2013, Lilly sought FDA approval for its own insulin-glargine product called Basaglar. Id. ¶¶ 4, 187-88. Lilly wanted to sell Basaglar on the U.S. market once the '722 patent had expired in February 2015. Id. ¶ 4. As is required by the FDA, Lilly notified Sanofi regarding the relationship between Basaglar and all of Sanofi's patents listed in the Orange Book for Lantus and Lantus SoloSTAR. Id. ¶ 191. With the exception of the '722 patent that Lilly was waiting to expire, Lilly notified Sanofi of its position that Sanofi's patents "were invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use, or sale of the Lilly . . . product." Id.

Sanofi sued Lilly for patent infringement on two of the vial formulation patents and two of the injector pen patents, including the '864 patent. Id. ¶ 205. Suit was brought within the statutorily mandated period of 45 days from receipt of Lilly's notice, thereby triggering an automatic stay of FDA approval of Basaglar for 30 months or until suit was resolved, whichever was sooner. Id. ¶ 206. The plaintiffs contend that this was "sham" litigation, and was brought without any basis and for the sole purpose of extending Sanofi's exclusive period. See, e.g., id. ¶¶ 224-34. As detailed below, this court concludes that the plaintiffs have failed to allege sufficient facts to support that conclusion.

Sanofi and Lilly engaged in extensive pre-trial litigation. See id. ¶ 238. On September 28, 2015, the morning of trial, Lilly and Sanofi settled the litigation. Id. ¶ 241. The settlement included an agreement that Sanofi would grant Lilly a royalty-bearing license so that Lilly could manufacture and sell Basaglar in a KwikPen device globally, and an agreement that Lilly would delay launching Basaglar in the United States until December 15, 2016, even if it obtained final FDA approval before then. Id. ¶¶ 241-43. Plaintiffs have defined the class period in this

litigation as February 13, 2015, when the '722 patent expired, through December 31, 2016, directly after when Lilly was able to sell Basaglar. Id. ¶ 284. Plaintiffs assert that they would have purchased Basaglar instead of Sanofi's products had it been available earlier, but, instead, were forced to buy Lantus and Lantus SoloSTAR products at arbitrarily-inflated prices. Id. ¶¶ 11-12, 250-59.

Regulatory Background[4]

New Drug Applications and Patent Listing Requirements

Drug manufacturers, including Sanofi and Lilly, must gain FDA approval before selling a drug in the United States. The requirements for doing so are listed in the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 *et seq*. ("FDCA"). Am. Compl. ¶ 27. Of relevance to the instant litigation, in connection with their applications for their insulin glargine products, Sanofi and Lilly were required to follow the processes for the approval of new drugs governed by § 505 of the FDCA ("§ 505"), which is codified at 21 U.S.C. § 355. Id. ¶ 28.

Applicants wishing to manufacture and sell a new drug must file a New Drug Application (an "NDA") under § 505(b)(1). Id. ¶ 29. The law mandates that an NDA applicant must submit scientific data demonstrating that a drug is safe and effective, as well as "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." § 505(b)(1); Am. Compl. ¶ 29. Within 30

[4] This court recognizes that the following description of the drug approval process is overly simplistic. It is intended just to highlight the aspects of the statutory scheme relevant to the instant motion to dismiss.

days of FDA approval of an NDA, or amendments or supplements thereto, or if the applicant obtains a new patent relating to the approved product, the applicant must provide the FDA with information regarding each patent that claims the "drug substance," "drug product," or "approved method of use" that falls within the statutorily defined listing requirements. See 21 C.F.R. § 314.53(b)(1); 21 U.S.C. §§ 355(b)(1) & (c)(2); see also Am. Compl. ¶¶ 43-45. The FDA publishes this information in the Orange Book, "so that competitors understand the scope of the brand's ostensible patent protection." See 21 U.S.C. § 355(c)(2); see also Am. Compl. ¶ 23.

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984), which amended the FDCA and whose provisions are known as the Hatch-Waxman Amendments. Am. Compl. ¶ 32. The Hatch-Waxman Amendments allowed for lower cost alternative brand products to come to market. Id. Under § 505(b)(2), as amended by the Hatch-Waxman Amendments, a brand company can file an NDA relying on data developed not by the applicant, but by a company with an already approved and sufficiently similar product. Id. ¶¶ 37, 38. In doing so, the applicant must certify the relationship between its product and the existing patents listed in the Orange Book on which the applicant is relying. § 505(b)(2); Am. Compl. ¶ 58. Specifically, § 505(b)(2) requires that when investigations relied on in the NDA "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted . . . [,]" an applicant can certify to either of four options: "(i) that such patent information has not been filed, (ii) that such patent has expired, (iii) of the date on which such patent will expire, or (iv) 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 . . . ." 21 U.S.C. § 355 (b)(2)(A)(i-iv); see Am. Com. ¶ 58.

When a company files an NDA with a certification under §505(b)(2)'s option IV (a "Paragraph IV Certification") claiming that the product will not infringe a patent or that the relevant patent is invalid, the patent statute treats the certification itself as a technical act of infringement. See 35 U.S.C. § 271(e)(2)(A). This allows the original company that listed the patent a chance to sue. If the patent holder sues the NDA applicant within 45 days of receiving the Paragraph IV Certification, the approval of the NDA is automatically stayed for 30 months, or until the litigation is resolved, whichever is sooner. See 21 U.S.C. §355(c)(3)(C).

Orange Book Listings Requirement

As noted above, 21 C.F.R. § 314.53 (b)(1) dictates which patents applicants must list in the Orange Book when filing an NDA. The regulation provides that applicants should list "patent[s] that claim[] the drug or a method of using the drug . . . [which] consist of drug substance (active ingredient) patents, **drug product (formulation and composition) patents**, and method-of-use patents." Section 314.53 also identifies those patents applicants should exclude, explaining that "[p]rocess patents [and] **patents claiming packaging** . . . are not covered by this section, and information on these patents must not be submitted to FDA." (Emphasis added).

In 2003, the FDA revised the regulations implementing certain statutory provisions included in the Hatch-Waxman Amendments. During the notice and comment period of the rulemaking process for those regulations, the FDA received various comments (hereinafter "Comments") regarding the proposed rule 21 C.F.R. § 314.53, which it summarized as follows:

> (Comment 3) Most comments agreed that patents claiming packaging should not be submitted for listing. However, some comments stated that patents claiming devices or containers that are "integral" to the drug product or require prior FDA approval should be submitted and listed. These comments distinguished between packaging and devices such as metered dose inhalers and transdermal patches, which are drug delivery systems used and approved in combination with a drug.

Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a New Drug is Invalid or Will Not Be Infringed, 68 Fed. Reg. 36676-01, 2003 WL 21391636, at 36,680 (June 18, 2003).

The FDA provided a response to the Comments with the final rule, noting that the agency had "clarified the rule to ensure that if the patent claims the drug product as defined in § 314.3, the patent must be submitted for listing."[5] Id. The FDA's response was as follows (hereinafter "FDA Response"):

> (Response) We agree that patents claiming a package or container must not be submitted. Such packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission. However, we have clarified the rule to ensure that if the patent claims the drug product as defined in § 314.3, the patent must be submitted for listing.
>
> Section 314.3 defines a "drug product" as "*** a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." **The appendix in the Orange Book lists current dosage forms for approved drug products**. **The list includes** metered aerosols, capsules, metered sprays, gels, and **pre-filled drug delivery systems**. **The key factor is whether the patent being submitted claims the finished dosage form of the approved drug product**. Patents must not be

[5] As detailed below, by purporting to "clarify" the issue, but not directly addressing the status of all "patents claiming devices or containers that are 'integral' to the drug product or require prior FDA approval[,]" the FDA caused confusion in the drug industry as to what types of product patents should be listed.

> submitted for bottles or containers and other packaging, as these are not "dosage forms."

Id. (emphasis added). At issue in connection with this motion to dismiss is whether Sanofi appropriately listed the '864 patent in the Orange Book. In particular, the plaintiffs contend that the '864 patent is just packaging and does not "claim[ ] the finished dosage form of the approved drug product." Sanofi contends that the '864 patent was appropriately listed as a pre-filled drug delivery system.

Sanofi's Products and Patents

Lantus

Sanofi is the holder of the original patent for insulin glargine, the '722 patent. Am. Compl. ¶ 103. Insulin glargine is a long-acting analog insulin for management of diabetes. Id. ¶ 3. The '722 patent expired in August 2014 with a period of pediatric exclusivity extending to February 2015. Id. ¶105. Sanofi listed the '722 Patent in the Orange Book. Id. ¶ 107.

On or around April 20, 2000, the FDA approved NDA No. 21-081 for Lantus, a sterile solution of insulin glargine for use as an injection and sold throughout the United States. Id. ¶¶ 3, 106, 108. As originally approved, Lantus "had two package forms: (1) vials (5 and 10 mL) for use with single-dose syringes, and (2) cartridges (3 mL) for use in an injector pen Sanofi called 'OptiPen™ One.'" Id. ¶ 110. Over the years, Sanofi obtained two additional "formulation" patents relating to the ingredients in the Lantus vial formulation. Id. ¶¶ 123, 126, 131-32. These were also listed in the Orange Book. Id. ¶ 154. Plaintiffs contend that these patents were improperly listed. Id. ¶¶ 155-58. However, since they are not the basis for Sanofi's motion to dismiss, they will not be discussed further herein.

Lantus SoloSTAR and the '864 Patent

In 2007, the FDA approved Sanofi to sell Lantus in another disposable injector pen called SoloSTAR. Id. ¶127. The letter from the FDA approving the NDA noted that "[t]his supplemental new drug application provides for the addition of the Lantus SoloStar disposable insulin injection device." Id. Ex. D.[6] As detailed above, Sanofi holds several patents relating to its injector pen products, including the '864 patent. See note 3, supra. The '864 patent, which is the only patent discussed in detail in the motion to dismiss, expires in 2024. Am. Compl. ¶ 163. That patent "relates to drive mechanisms suitable for use in drug delivery devices, in particular pen-type injectors, having dosage setting means, enabling the administration of medicinal products from a multi-dose cartridge. In particular, the present invention relates to such drug delivery devices where a user may set the dose." Id. Ex. I ('864 patent) at Technical Field section, col. 1, ll. 18-23.[7]

It is undisputed that Lantus SoloSTAR is sold loaded with a dosage of insulin glargine. See, e.g., Am. Compl. ¶¶ 128-29. The FDA approval obviously contemplated a pre-filled device, as evidenced by the warnings it required on the Lantus SoloSTAR carton relating to the condition of the enclosed solution. Id. Ex. D. However, the '864 patent itself does not mention Lantus or insulin glargine. It also does not expressly require that the dispenser be pre-filled.

[6] While the plaintiffs alleged that the FDA approved Lantus SoloSTAR as a "package change," Am. Compl. ¶127, the approval letter from the FDA (attached to the complaint) makes it clear that it was approved as a "disposable insulin injection device." Id. Ex. D. Plaintiffs have not continued to argue that the FDA just approved a package change.

[7] While both parties have asked the court to review the '864 patent, the Amended Complaint contains no allegations as to the correct interpretation of the patent. Nothing herein is intended to constitute a construction of any of the terms of the patent. Rather, the description of the patent terms contained herein is based only on the plain language of the patent.

Nevertheless, the invention claimed is "[a] drive mechanism for use in a drug delivery device" which device includes a "dose dial sleeve" and a "dose limiting mechanism." See, e.g., id. Ex. I at Claims 1, 2 & 5. The "Background" section of the patent makes it clear that the drug delivery device is used for "regular injection[s] by persons without formal medical training[,]" such as in connection with the management of diabetes. Am. Compl. Ex. I. At issue in this litigation is whether the patents for the Lantus SoloSTAR (including its components) are appropriately listed in the Orange Book as a "drug product." While both parties rely on the Comments and FDA Response generated during rulemaking (as quoted above), the plaintiffs argue that the listing was improper because the patent did not "claim[ ] the finished dosage form of the approved drug product" and was just for packaging. Sanofi, on the other hand, argues that the listing was proper because the Lantus SoloSTAR is a "pre-filled drug delivery device" and the patent otherwise relates to an approved drug product. As detailed below, this court finds that while the issue of whether the Lantus SoloSTAR patent is appropriately listed in the Orange Book is an open question, Sanofi's interpretation is reasonable and, therefore, defeats the plaintiffs' antitrust claims.

Lilly's Competing Product

Lilly developed Basaglar, an insulin-glargine product similar to Sanofi's, which Lilly planned to use with its injector pen product KwikPen. Am. Compl. at ¶¶ 185-88. Like the Lantus SoloSTAR, the KwikPen had been approved by the FDA. Id. ¶ 186. In 2013, Lilly filed an NDA under § 505(b)(2). Id. ¶ 187. Lilly sought approval to sell Basaglar in the U.S. upon the expiration of Sanofi's '722 patent's pediatric exclusivity period. Id. ¶¶ 187, 192. Lilly's application relied on Sanofi's previous NDA for Lantus as well as the studies associated

therewith, as is allowed by the Hatch-Waxman Amendments. Id. ¶ 188. "These studies established a 'bridge' between Basaglar and Lantus to demonstrate that Basaglar was sufficiently similar to Lantus such that reliance on Lantus studies was scientifically justified." Id.

As part of its NDA, Lilly filed Paragraph IV Certifications regarding Sanofi's formulation patents and injector pen patents. In doing so, Lilly certified that those Sanofi patents "were invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use, or sale" of Basaglar. Id. ¶ 191. "Lilly filed a paragraph III certification as to the '722 patent, agreeing to wait to market [Basaglar] until that patent expired." Id.

After receipt of the paragraph III and IV certifications, Lilly and Sanofi signed a confidential access agreement and Sanofi received 66 pages of Lilly's NDA. Id. ¶¶ 201-02. The confidential documents identified for Sanofi the active and inactive ingredients of Basaglar and Lilly's associated injector pen. Id. ¶¶ 202, 204. According to the plaintiffs, but denied by Sanofi, "[t]he documents showed that the Lilly NDA product would not infringe any of the claims [in] the two injector pen patents (the '864 and '044 patents) or any claims in the two vial formulation patents (the '652 and '930 patents)." Id. ¶ 204.

The Lawsuit

In January 2014, Sanofi sued Lilly for infringement based on these formulation and injector pen patents. Id. ¶ 205.[8] The lawsuit was brought within 45 days of Sanofi's receipt of Lilly's Paragraph IV Certification. Id. ¶ 206. As a result of filing the lawsuit, as provided for by

[8] In March 2014, the PTO issued U.S. Patent No. 8,679, 069 ("the '069 patent"), another injector pen patent. Am. Compl. ¶ 221. Sanofi amended the complaint to include infringement claims regarding the '069 patent. Id. ¶ 223.

21 U.S.C. §355(c)(3)(C), FDA approval for Basaglar was automatically stayed for 30 months, or the conclusion of the litigation, whichever was sooner. Id.

Through its lawsuit, "Sanofi sought to have Lilly enjoined 'from engaging in any commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of the insulin glargine [rDNA origin] injection in a prefilled insulin delivery device, 100 units/mL as claimed by the Patents-in-Suit for the full terms thereof (and any additional period of exclusivity to which Plaintiffs and/or the Patents-in-Suit are, or become, entitled), and from inducing or contributing to such activities.'" Am. Compl. ¶ 215. Lilly denied the claims of infringement, asserted affirmative defenses of patent misuse and prosecution laches, counterclaimed seeking declarations of non-infringement, invalidity, and non-enforceability of the patents for patent misuse and prosecution laches, and sought an order removing the '864 and '044 Patents from the Orange Book. Id. ¶ 217.

With respect to the '864 patent in particular, the plaintiffs allege that Sanofi brought suit "even though, after reviewing the materials Lilly provided, its lawyers had no basis to conclude that Lilly's KwikPen was covered by any claim of the '864 patent." Id. ¶ 212. However, other than stating that the KwikPen was "different" than and was not the same "type" as the Lantus SoloSTAR, the plaintiffs have not alleged any facts to establish that the KwikPen does not infringe on Sanofi's patents. See, e.g., id. ¶¶ 231-33.

The Sanofi/Lilly dispute was actively litigated. As described by the plaintiffs, the parties "engaged in substantial discovery, including interrogatories and document requests; sub-poenaed non-parties; fought multiple discovery disputes; tendered experts and submitted . . . Daubert motions opposing those experts; and undertook the nuanced and complex process of

claim construction" albeit, according to the plaintiffs, relating to some irrelevant claims. Id. ¶ 238. On September 28, 2015, the morning that trial was set to begin, Lilly and Sanofi settled their suit. Id. ¶ 241. Under the settlement, Sanofi granted Lilly a royalty-bearing license that allowed Lilly to sell Basaglar in the KwikPen device upon the payment of royalties. Id. The settlement also "memorialized Lilly's agreement to stall its Basaglar launch until December 15, 2016 . . . [and] provided the FDA with authority to grant final approval to Lilly's Basaglar NDA." Id. ¶ 242.

Approval of Basaglar

The FDA had granted tentative approval for Basaglar in August 2014. Id. ¶ 236. Plaintiffs contend that were it not for "Sanofi's wrongful Orange Book listings, or Sanofi's filing of the frivolous patent litigation, the FDA would have granted Lilly final approval for Basaglar as soon as the '722 patent's pediatric exclusivity expired in February 2015." Id. ¶ 237. Instead, the FDA granted final approval for Basaglar on December 16, 2015. Id. ¶ 244. In accordance with its settlement with Sanofi, Lilly could not launch Basaglar for another year, until December 15, 2016. Id. ¶ 247.

Alleged Harm

Plaintiffs seek to bring suit on behalf of a proposed class of purchasers who claim to have paid higher prices for insulin glargine products between February 2015 and December 2016 as a result of Sanofi's anticompetitive behavior. See id. ¶¶ 11-12, 284. Plaintiffs claim that the loss to American purchasers during the delay caused by the lawsuit "would have far exceeded a billion dollars." Id. ¶ 9. They allege that were it not for "Sanofi's anticompetitive conduct, the plaintiffs and other members of the class would have: (1) purchased lower-priced

insulin glargine products instead of the higher-priced Lantus and Lantus SoloSTAR products for some or all of their insulin glargine needs; (2) paid a lower price for their insulin glargine products, sooner; and/or (3) paid lower prices for some or all of their remaining purchases." Id. ¶ 254.

Additional facts are included below as necessary.

III. LEGAL STANDARD

A. Standard of Review – Motion to Dismiss for Failure to State a Claim

Motions to dismiss under Rule 12(b)(6) test the sufficiency of the pleadings. When confronted with such a motion, the court accepts as true all well-pleaded facts and draws all reasonable inferences in favor of the plaintiff. See Cooperman v. Individual Inc., 171 F.3d 43, 46 (1st Cir. 1999). The court may also consider "implications from documents attached to or fairly incorporated into the complaint . . . facts susceptible to judicial notice . . . [and] concessions in plaintiff's response to the motion to dismiss." Schatz v. Republican State Leadership Comm., 669 F.3d 50, 55-56 (1st Cir. 2012) (internal quotations and citations omitted).

As the First Circuit has explained, in considering the merits of a motion to dismiss, the court proceeds in two steps. First, we "isolate and ignore statements in the complaint that simply offer legal labels and conclusions or merely rehash cause-of-action elements." Id. at 55. Second, we "take the complaint's well-pled (*i.e.*, non-conclusory, non-speculative) facts as true, drawing all reasonable inferences in the pleader's favor, and see if they plausibly narrate a claim for relief." Id. Dismissal is only appropriate if the complaint, so viewed, fails to allege "a plausible entitlement to relief." Rodriguez-Ortiz v. Margo Caribe, Inc., 490 F.3d 92, 95 (1st Cir. 2007) (quoting Bell Atl. Corp. v. Twombly, 550 U.S. 544, 559, 127 S. Ct. 1955, 1967, 167 L. Ed. 2d

929 (2007)). "Plausible . . . means something more than merely possible[.]" Schatz, 669 F.3d at 55. "The bottom line is that the combined allegations, taken as true, must state a plausible, not merely conceivable, case for relief." Carrero-Ojeda v. Autoridad de Energia Electrica, 755 F.3d 711, 718 (1st Cir. 2014) (internal citations and quotations omitted). "Engaging in this plausibility inquiry is 'a context-specific task that requires the reviewing court to draw on its judicial experience and common sense.'" Germanowski v. Harris, 854 F.3d 68, 72 (1st Cir. 2017) (quoting Ashcroft v. Iqbal, 556 U.S. 662, 679, 129 S. Ct. 1937, 1950, 173 L. Ed. 2d 868 (2009)).

B. Standard for Monopolization and Attempted Monopolization Under the Sherman Act

Plaintiffs bring two counts under the Sherman Act, 15 U.S.C. § 2, one for monopolization and the other for attempted monopolization. Am. Compl. ¶¶ 294-309. In order to be successful on a claim under § 2 of the Sherman Act, a plaintiff must "demonstrate (1) that the defendant possesses monopoly power in the relevant market, and (2) that the defendant has acquired or maintained that power by improper means." Town of Concord, Mass. v. Boston Edison Co., 915 F.2d 17, 21 (1st Cir. 1990) (internal quotations and citations omitted). "[A] practice, a method, a means, is 'improper' if it is 'exclusionary.' To decide whether [a company's] conduct was exclusionary, we should ask whether its dealings with [a competitor] went beyond the needs of ordinary business dealings, beyond the ambit of ordinary business skill, and 'unnecessarily excluded competition' from the [] market." Barry Wright Corp. v. ITT Grinnell Corp., 724 F.2d 227, 230 (1st Cir. 1983) (internal citations omitted). Thus, successful claims of monopolization must establish "that the defendant 'has engaged in impermissible 'exclusionary' practices with the design or effect of protecting or enhancing its monopoly position.'" Boston Scientif Corp. v. Schneider (Europe) AG, 983 F. Supp. 245, 268 (D. Mass.

1997) (quoting Coastal Fuels of P.R., Inc. v. Caribbean Petroleum Corp., 79 F.3d 182, 195-96 (1st Cir. 1996)). "In other words, the acquisition and maintenance of the power must be willful, rather than a result of legitimate means such as patents, superior products, business acumen, or historic accident." Id. Finally, "[a]ttempted monopolization under § 2 of the Sherman Act requires proof of (1) anti-competitive or exclusionary conduct; (2) specific intent to monopolize; and (3) a dangerous probability that the attempt will succeed. Id. and cases cited.

IV. ANALYSIS

As detailed herein, on the non-conclusory facts alleged, plaintiffs have not presented a plausible case for relief under the Sherman Act with regard to either the claim of improper Orange Book listings or of sham litigation. The court will address each in turn. Sanofi has also moved to dismiss the Amended Complaint on the grounds that the plaintiffs have failed to allege the relevant market and, hence, have failed to establish that Sanofi possessed monopoly power. Sanofi informed the court during oral argument that it would not pursue this ground if it prevails on its other arguments. Since this court concludes that the plaintiffs have failed to plead an improper means of acquiring monopoly power, this court will not address the arguments regarding whether plaintiffs have adequately pled that Sanofi possessed monopoly power in the relevant market.

A. The Orange Book Listing of the '864 Patent

As detailed above, one of the purposes of the Orange Book "is to provide would-be generic manufacturers with notice of any patent rights that are implicated by a brand-name drug." United Food & Comm. Workers Unions & Employers Midwest Health Befits Fund v. Novartis Pharm. Corp., Civil Action No. 15-cv-12732, 2017 WL 2837002, at *5 (D. Mass. June 30,

2017) (hereinafter "United Food"). Applicants are "required by law" to identify "any patent that 'claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.'" In re Buspirone Patent Litig., 185 F. Supp. 2d 363, 371 (S.D.N.Y. 2002) (quoting 21 U.S.C. § 355(b)(1)). For its part, the FDA is required by law to publish the information provided by the applicant in the Orange Book. Id. (citing 21 U.S.C. 355(b)(1) & (c)(2)). Thus, "[t]he FDA does not independently determine whether a particular drug product actually reads on a particular patent claim, and it does not examine the asserted patents to ensure their validity." United Food, 2017 WL 2837002, at *6.

It is undisputed that "listing presumptively valid patents in the Orange Book and enforcing them against infringers are not bases for an antitrust claim; Orange Book listing is a statutory obligation and enforcement is a statutory right." In re Lipitor Antitrust Litig., MDL No. 2332, 2013 WL 4780496, at *21 (D.N.J. Sept. 5, 2013); see also In re Solodyn (Minocylcine Hydrochloride) Antitrust Litig., No. 14-md-02503-DJC, 2015 WL 5458570, at *12 (D. Mass. Sept. 16, 2015) (since patent was never held to be invalid or unenforceable and defendant was required by statute to submit its patents for listing in the Orange Book, the listing in and of itself could not form the basis for a Section 2 claim). Nevertheless, improperly listing a patent in the Orange Book may subject the patent holder to antitrust liability. See Buspirone, 185 F.

Supp. 2d at 372-73 (conduct in providing information for listing in Orange Book is "not immune from liability under the Sherman Act.").[9]

A defendant may be found to have acquired or maintained monopoly power by improper means if the defendant engaged in unambiguously wrongful conduct that resulted in the improper listing of patents in the Orange Book. See, e.g., In re Remeron Antitrust Litig., 335 F. Supp. 2d 522, 529-30 (D.N.J. 2004) (motion to dismiss antitrust claim denied where defendant filed its Orange Book listing more than a year after the 30 day period required by FDA regulations and plaintiffs alleged a scheme to delay generic competition); Buspirone, 185 F. Supp. 2d at 374, 376 (antitrust claim based on improper listing allowed to proceed where the defendant had affirmatively misrepresented to the FDA that a patent covered uses which the defendant itself had abandoned in the approval process). On the other hand, if an applicant "had a reasonable basis for the submission," then the listing does not constitute improper means for antitrust purposes. See Organon, Inc. v. Mylan Pharm., Inc., 293 F. Supp. 2d 453, 460 (D.N.J. 2003) (given ambiguities in statutory and regulatory language, applicant had a "reasonable basis" to list patent in Orange Book; motion to dismiss antitrust claim based on improper listing allowed); see also Buspirone, 185 F. Supp. 2d at 374, 376 (standard to be applied is whether the listing was "objectively baseless").

[9] Under the Noerr-Pennington doctrine, as articulated in E. R.R. Presidents Conference v. Noerr Motor Freight, Inc., 365 U.S. 127, 81 S. Ct. 523, 5 L. Ed. 2d 464 (1961), and United Mine Workers of Am. v. Pennington, 381 U.S. 657, 85 S. Ct. 1585, 14 L. Ed. 2d 626 (1965), "petitioning activity ... is generally immune from suit under the Sherman Act." Buspirone, 185 F. Supp. 2d at 368. Courts have held that unlike litigation, which is protected, submitting information for the Orange Book is not petitioning activity. Id. at 372-73. Since this principle is not in dispute here, no extended discussion is warranted.

Based, in part, on their original contention that the FDA approved the Lantus SoloSTAR as a "package change," the plaintiffs alleged in their Amended Complaint that it was obvious that the '864 patent should not have been listed in the Orange Book. Am. Compl. ¶ 127. See note 6, supra. Given the clear instructions by the FDA that patents for packaging should not be listed, this allegation may have been sufficient to survive a motion to dismiss. However, the record is now clear that the Lantus SoloSTAR was approved as a drug delivery system, and not merely as a package. Am. Compl. Ex. D. Therefore, further analysis is needed.

The FDA has expressly interpreted "drug products" which must be listed in the Orange Book to include "pre-filled drug delivery systems." As the plaintiffs recognized in their Amended Complaint, Lantus SoloSTAR was, in fact, sold as a pre-filled drug delivery system. Am. Compl. ¶¶ 127-29. The FDA approval for the Lantus SoloSTAR also contemplated that it would be sold as a pre-filled drug delivery system. Id. Ex. D. Therefore, it was not unreasonable for Sanofi to believe that it should list the Lantus SoloSTAR, and its components, in the Orange Book.

Moreover, an argument can be made that listing the Lantus SoloSTAR and its components is consistent with the purposes of the Orange Book, which is to put others on notice of potentially relevant patents. As plaintiffs have alleged in the Amended Complaint, Lilly's competitive products included both a drug and a drug delivery system. Therefore, the patents relating to the drug delivery system would be relevant to determining whether Lilly's products were subject to patent infringement claims.

It is also significant that the Lantus SoloSTAR is clearly not just a package, or container to hold a drug, but rather is an integral part of the way insulin glargine can be used to treat

diabetes. Therefore, while it may be debatable whether the Lantus SoloSTAR fits neatly into the category of patents that must be disclosed, it does not fit into the category of patents that must not be disclosed.

In arguing against the above conclusion, plaintiffs contend that the '864 patent should not have been listed in the Orange Book because the FDA stated in its Response to Comments quoted above that "the key factor is whether the patent being submitted claims the finished dosage form of the approved drug product" and there is no such "claim" in the '864 patent. See Am. Compl. ¶¶ 171-72. Although the requirement for such an express claim is not detailed in the regulations themselves, this court recognizes that it must give significant deference to an agency interpretation of its own regulations. Fed. Energy Regulatory Comm'n v. Silkman, 177 F. Supp. 3d 683, 711 (D. Mass. 2016) (finding that the court "must accept the reasonable interpretation of an ambiguous provision by the agency delegated authority to make that interpretation.") (relying on U.S. v. Mead Corp., 533 U.S. 218, 226-27, 121 S. Ct. 2164, 2171, 150 L. Ed. 2d 292 (2001))). However, the Response itself is ambiguous, and does not directly address the Comments, which concerned all delivery devices "that are 'integral' to the drug product or require prior FDA approval[.]" See note 5, supra. Moreover, even assuming such a "claim" must be made in the patent, it is not clear whether or not the "claims" of the '864 patent, which are for a drug delivery device which includes a dose dial sleeve and a dose limiting mechanism, among other things, are sufficient to satisfy any such requirement. In sum, regardless which party's interpretation would ultimately be accepted by the FDA, the plaintiffs have not pled sufficient facts to establish that Sanofi's decision to list the '864 patent in the Orange Book was unreasonable or objectively baseless.

This conclusion is bolstered by the fact that Sanofi is not alone in its interpretation of the FDA listing requirements. Sanofi has submitted publicly available evidence that on six different occasions from 2005 to 2012, companies have written to the FDA inquiring about the correct interpretation of the listing requirements.[10] Plaintiffs conceded at oral argument that there are no other relevant inquiries or responses that the court should consider. These inquiries show that the question asked of the FDA during its rulemaking comment period, i.e., should all patents for "containers that are 'integral' to the drug product or require prior FDA approval" be submitted to the Orange Book, remains unanswered. See note 5, supra. The FDA's "clarification" in response to these Comments left a significant ambiguity.

[10] "The court may judicially notice a fact that is not subject to reasonable dispute because it: (1) is generally known within the trial court's territorial jurisdiction; or (2) can be accurately and readily determined from sources whose accuracy cannot reasonably be questioned." FRE 201(b). "The court: (1) may take judicial notice on its own; or (2) must take judicial notice if a party requests it and the court is supplied with the necessary information." Fed. R. Evid. 201(c). The court hereby takes judicial notice of the following requests for clarification with regard to the fact that they contain a question for the FDA, not for the truth of their contents. See OrbusNeich Med. Co., Ltd., BVI v. Boston Scientific Corp., 694 F. Supp. 2d 106, 111 (D. Mass. 2010) ("The public filing of [a] document with a regulatory agency [] makes it a proper subject of judicial notice, at least with regard to the fact that it contains certain information, though not as to the truth of its contents."). The court takes notice of: (1) Request for Advisory Opinion on behalf of GSK, Docket No. FDA-2005-A-0476 (Jan. 10, 2005), available at https://www.regulations.gov/document?D=FDA-2005-A-0476-0003; (2) Request for Advisory Opinion by Ropes & Gray, Docket No. FDA-2006-A-0063 (Aug. 10, 2006), available at https://www.regulations.gov/document?D=FDA-2006-A-0063-0005; (3) Request for Advisory Opinion on behalf of AstraZeneca, Docket No. FDA-2007-A-0099 (June 21, 2007), available at https://www.regulations.gov/document?D=FDA-2007-A-0099-0003; (4) Letter on behalf of GSK, Docket No. FDA-2005-A-0476 (Feb. 11, 2009), available at https://www. regulations.gov/document?D=FDA-2005-A-0476-0004; (5) Request for Advisory Opinion on behalf of Forest Laboratories, Docket No. FDA-2011-A-0363 (May 12, 2011), available at https://www.regulations.gov/document?D=FDA-2011-A-0363-0001 as well as responses thereto; (6) Letter from FDA to Forest Laboratories, Docket No. FDA-2011-A-0363-0008 (Nov. 7, 2011), available at https://www.regulations.gov/document?D=FDA-2011-A-0363-0008; (7) Request for Advisory Opinion on behalf of Novo Nordisk, Docket No. FDA-2012-A-1169 (Nov. 26, 2012), available at https://www.regulations.gov/document ?D=FDA-2012-A-1169-0001.

Since at least 2005, drug manufacturers have sought to determine whether patents directed to drug delivery systems that do not recite the approved active ingredients or formulation should be listed in the Orange Book. See note 10, supra. In the absence of any response to several inquiries to the FDA, in 2007, AstraZeneca informed the FDA that it was going to continue to list in the Orange Book patents for approved pre-filled drug delivery systems even if the patent neither disclosed nor claimed the active ingredient or formulation of the approved drug product. Request for Advisory Opinion on behalf of AstraZeneca, Docket No. FDA-2007-A-0099 (June 21, 2007), available at https://www.regulations.gov/document?D=FDA-2007-A-0099-0003. Similarly, in 2009, GlaxoSmithKline ("GSK") wrote to the FDA informing the agency that "in the absence of further guidance from the FDA, [GSK] has modified its Orange Book listing practice to list those patents . . . that claim all or a portion of integrated drug-device products, regardless of whether the approved drug substance is specifically mentioned in the claims of such patents." Letter from GSK to FDA, Docket No. FDA-2005-A-0476 (Feb. 11, 2009), available at https://www.regulations.gov/document?D=FDA-2005-A-0476-0004. In 2011, in response to an inquiry from Forest Laboratories, Inc., the FDA wrote that "due to the need to address other Agency priorities," it "has been unable to reach a decision" on "whether a patent that claims a drug delivery device whose use is integral to the administration of the active ingredient and the approval of the NDA, but that does not claim the active ingredient of the approved drug product, should be submitted for listing in [the Orange Book]." Interim Response to Forest Laboratories, Inc., Docket No. FDA-2011-A-0363 (Nov. 7, 2011), available at https://www.regulations.gov/document?D=FDA-2011-A-0363-0008. No further response was received from the FDA and, in 2012, Novo Nordisk again asked for an advisory opinion, and, like

others before it, notified the FDA that it intended to list patents in the Orange Book for pre-filled drug delivery systems "regardless of whether or not the patents disclose or claim the active ingredient or formulation of the approved drug product."[11] Request for Advisory Opinion, Docket No. FDA-2012-A-1169 (Nov. 26, 2012), available at https://www.regulations.gov/ document?D=FDA-2012-A-1169-0001. Again there was no response from the FDA. Thus, by the time of Lilly's Paragraph IV Certification, the FDA had been informed that a number of drug manufacturers were listing their drug delivery systems in the Orange Book, even if the relevant patents did not claim "the finished dosage form of the approved drug product," but had not indicated that such a listing was improper. The fact that the FDA did not cite to its Response, but, rather, stated that "it had been unable to reach a decision" compels the conclusion that the question whether a patent for a delivery system must claim "the finished dosage form of the approved drug product" was not answered in the Response, and remains an open question.

While this court makes no determination as to the correct interpretation of the FDA Comments, it is clear from these requests that the issue whether the '864 patent should have been listed is an open question in the industry. For the reasons detailed herein, Sanofi's interpretation of the listing requirements was reasonable. The plaintiffs have pled no other facts that lead to the conclusion that Sanofi knew or should have known that its listing of the '864 patent was incorrect. Therefore, the Sherman Act claims, insofar as they rely on the improper Orange Book listing of the '864 patent, are dismissed.

[11] As described in the letter to the FDA, this was a change in its position – before then, Novo Nordisk had not listed such patents in the Orange Book.

B. The Sham Litigation Claim

Plaintiffs also contend that Sanofi sought to wrongfully extend its exclusionary period by "[c]ommencing and maintaining a sham litigation against Lilly to delay introduction of competing insulin glargine products into the U.S. market." Am. Compl. ¶ 296. Once Lilly filed its Paragraph IV Certification in its NDA, Sanofi had the statutory right to sue under 35 U.S.C. § 271(e)(2)(A) in order to enforce its patent. See Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1568-69 (Fed. Cir. 1997). The Paragraph IV Certification is deemed to be "a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity." Id. at 1569. However, "[t]he occurrence of the defined 'act of infringement' does not determine the ultimate question whether what will be sold will infringe any relevant patent." Id. Thus, while a patent holder has the right to bring patent infringement litigation upon receipt of a Paragraph IV Certification, it is not obligated to do so.

The filing of a lawsuit is generally protected activity under the First Amendment, as recognized by the Noerr-Pennington doctrine. See note 9, supra. However, immunity is lost if the lawsuit is a "sham." See In re Solodyn (Minocycline Hydrochloride) Antitrust Litig., 2015 WL 5458570, at *11 ("Under the Noerr-Pennington doctrine, filing a lawsuit is protected under the First Amendment unless the lawsuit is a 'sham.'") (citing Prof'l Real Estate Investors, Inc. v. Columbia Pictures Indus., Inc., 508 U.S. 49, 56, 60-61, 113 S. Ct. 1920, 1926, 1928, 123 L. Ed. 2d 611 (1993))). In the instant case, plaintiffs contend that Sanofi had no reasonable belief that Basaglar or its KwikPen infringed its patents when initiating the lawsuit against Lilly. However,

as detailed herein, the allegations of the Amended Complaint are insufficient to state a claim for sham litigation.

The Supreme Court has identified a two-part definition for sham litigation.

> First, the lawsuit must be objectively baseless in the sense that no reasonable litigant could realistically expect success on the merits. If an objective litigant could conclude that the suit is reasonably calculated to elicit a favorable outcome, the suit is immunized under Noerr, and an antitrust claim premised on the sham exception must fail. Only if the challenged litigation is objectively meritless may a court examine the litigant's subjective motivation. Under this second part of our definition of sham, the court should focus on whether the baseless lawsuit conceals an attempt to interfere directly with the business relationships of a competitor. . . .

Prof'l Real Estate Investors, Inc., 508 U.S. at 60 (internal quotations and emphasis omitted). "Only if the suit is found to be objectively baseless may the court proceed to the second prong of the test." Morton Grove Pharm. v. Par Pharm. Cos., Inc., 2006 WL 850873, at *10 (N.D. Ill. 2006).

Specific to the '864 patent, the plaintiffs make two principal claims in support of their sham litigation argument. First, the plaintiffs claim that Sanofi initiated litigation while knowing that Lilly's KwikPen did not infringe the '864 patent. Second, the plaintiffs contend that Sanofi sued on the '864 patent knowing that the patent should not have been listed in the Orange Book to begin with. As the court has already dismissed the Orange Book listing claim, the plaintiffs' second argument need not be addressed further.

The Facts as Alleged do not Establish that the Lawsuit was "Objectively Baseless"

"A firm that has received a patent from the patent office (and not by fraud . . .), and thus enjoys the presumption of validity that attaches to an issued patent . . . is entitled to defend the patent's validity in court, to sue alleged infringers, and to settle with them,

whatever its private doubts, unless a neutral observer would reasonably think either that the patent was almost certain to be declared invalid, or the defendants were almost certain to be found not to have infringed it, if the suit went to judgment." United Food, 2017 WL 2837002, at *11 (quoting Asahi Glass Co. v. Pentech Pharm., Inc., 289 F. Supp. 2d 986, 992-93 (N.D. Ill. 2003)). Thus, to prevail on its sham litigation claim, the plaintiffs must establish that Sanofi "had no reasonable basis to believe that its patent claims were valid or that they were infringed by [Lilly.]" 800 Adept, Inc. v. Murex Sec., Ltd., 539 F.3d. 1354, 1370 (Fed. Cir. 2008), and cases cited. Here, however, the facts as alleged do not show that Lilly was "almost certain to be found not to have infringed" the '864 patent. United Food, 2017 WL 2837002, at *11.

According to the Amended Complaint, prior to bringing suit Sanofi had "[t]he pages of Lilly's § 505(b)(2) application [that] (1) showed the list of ingredients of Lilly's NDA product, and (2) identified the type of injector pen by which the Lilly NDA product would be administered." Am. Compl. ¶ 204. Other than repeatedly stating that the documents showed that Lilly's products "would not infringe any of the claims in the two injector pen patents (the '864 and '044 patents) or any claims in the two vial formulation patents (the '652 and '930 patents)[,]" the plaintiffs have offered no facts in support of these conclusions. Id. ¶¶ 204, 211-12, 231-33. Since this court must disregard conclusory allegations of fact and law, Schatz, 669 F.3d at 55, the allegations of the Amended Complaint are insufficient to show that the underlying lawsuit lacked any reasonable merit.

Other facts also support the conclusion that the lawsuit was not objectively baseless.[12] While none of these facts, in and of themselves, establish that the litigation brought by Sanofi was not sham litigation, they all combine to defeat any contention that the litigation was objectively unreasonable when brought. See United Food, 2017 WL 2837002, at *10-13 (finding that plaintiffs fail to sufficiently plead sham litigation after considering multiple factors); AstraZeneca AB v. Mylan Labs., Inc., MDL Docket No. 1291, 2010 WL 2079722, at *4 (S.D.N.Y. May 19, 2010) (finding that suit was not a sham based on an analysis of the extent of the underlying litigation and because a Paragraph IV Certification gave "an objectively reasonable basis to sue.").

As an initial matter, in its litigation with Lilly, Sanofi was enforcing patents that had never been invalidated or found unenforceable against an obvious act of infringement. While this is not a prerequisite to a claim of sham litigation, it is not irrelevant: patents are presumed to be valid, and patent holders are entitled to enforce their rights under their patents, so parties claiming sham litigation must overcome these presumptions. See United Food, 2017 WL 2837002, at *10 ("The Court declines to adopt a bright-line rule requiring that a patent be invalidated or tarnished before a plaintiff can allege a sham litigation claim, but notes that it is difficult to conceive of a scenario in which a sham litigation claim would go forward without the patent having been invalidated or otherwise tarnished."). Moreover, with respect to the '864 patent, as detailed above, there was industry support for the proposition that such patents

[12] The court may take judicial notice of the docket of any court case. Maher v. Hyde, 272 F.3d 83, 86 n.3 (1st Cir. 2001). Here the underlying case is found at Sanofi-Aventis U.S. LLC v. Eli Lilly & Co., No. 1:14-cv-00113-RGA-MPT (D. Del.) ("Sanofi I").

should be listed in the Orange Book. Thus, the fact that Sanofi sought to protect the '864 patent in the face of a Paragraph IV Certification is not obviously unreasonable.

Moreover, the record in the underlying litigation establishes that Sanofi's contention that the KwikPen infringed on the '864 patent was not objectively baseless. As detailed above, the plaintiffs' assertion that there was no infringement is not supported by any facts in the Amended Complaint. In contrast, the parties in Sanofi I engaged in a claim construction dispute addressing various elements of the '864 patent. If Lilly's KwikPen was completely different, and bore no relationship to the Lantus SoloSTAR (as plaintiffs allege) there would have been no reason for Lilly to have participated in a claims construction exercise. Instead, both Lilly and Sanofi proposed different interpretations of various elements of the '864 patent, and the court adopted and rejected some of each of the parties' suggestions. See Sanofi I, Docket No. 192. The record does not support the conclusion that Sanofi should have known that there was no way that Lilly's KwikPen could be found to have infringed on Sanofi's product.

The fact that the underlying litigation was heavily contested, while not conclusive, also weighs against a finding that the litigation was a sham. The '864 patent was litigated for over a year and a half before the parties came to a settlement agreement on the eve of trial. The docket indicates an active and hard-fought dispute. The sham litigation exception to the Noerr-Pennington immunity was not intended to provide all third parties with an opportunity to re-litigate cases. Rather, the doctrine is reserved for those cases where plaintiffs can assert facts showing that the patent suit was objectively meritless. See AstraZeneca AB, 2010 WL 2079722, at *4 (finding that the underlying lawsuit was "hard-fought and close" and that such an "outcome hardly bespeaks baseless litigation."); see also Asahi Glass Co., Ltd., 289 F. Supp. 2d

at 995 (". . . to avoid turning every patent case into an antitrust case, some threshold of plausibility must be crossed at the outset before a patent antitrust case should be permitted to go into its inevitably costly and protracted discovery phase . . . an infringement suit must be adjudged to be objecttively baseless before it can be considered an unlawful method of competition . . ."). The fact that Sanofi I was litigated so extensively before settlement is evidence that the claims involved were not baseless.

The settlement in Sanofi I, while not dispositive, further shows that the underlying suit did not lack any merit. See Toyo Tire & Rubber Co., Ltd. v. Atturo Tire Corp., No. 14 C 0206, 2017 WL 1178224, at *4 (N.D. Ill. Mar. 30, 2017) (". . . courts have invariably held that lawsuits terminating in favorable settlement are also objectively reasonable and are not shams"). Obviously "[p]arties may settle a litigation for a variety of reasons independent of the merits of the claims." Morton Grove, 2006 WL 850873, at *11 (internal citations omitted). Nevertheless, a "favorable prior settlement may afford support for a belief that subsequent litigation will be successful[.]" Id. Here, plaintiffs argue that the settlement was not, in fact, a "favorable" one since it allowed Lilly to enter the market many years before all of the relevant patents expired. However, Sanofi points to the fact that it is going to be paid royalties from Lilly in connection with the sale of Lilly's products, and that the settlement delayed Lilly's entry into the market until December 2016. Given the existence of the royalty payments, and the delayed entry into the market, it cannot be said that the settlement was so insignificant that the underlying

litigation was obviously a sham. Rather, the fact of the settlement helps defeat a finding that the litigation was objectively baseless.[13]

In light of the plaintiffs' failure to establish that the litigation was objectively baseless, this court need not address the second prong of the sham litigation test. Accordingly, plaintiffs' antitrust claims based on a contention of sham litigation are dismissed.

C. Plaintiffs' Other Claims Fail for Lack of Causation

In light of the court's conclusion that the litigation concerning the '864 patent was not a sham litigation, the remainder of the claims of the Amended Complaint relating to the other Sanofi patents must be dismissed. Since Sanofi was entitled to bring its patent litigation against Lilly due to the '864 patent, Sanofi was entitled to the 30 month delay in Lilly's entry into the market.

"An antitrust plaintiff must prove a causal connection between the antitrust violation and actual damages suffered." In re Wellbutrin XL Antitrust Litig., 2012 WL 1657734, at *33 (E.D.P.A. May 11, 2012). In an antitrust class action, "individual injury (also known as antitrust impact) is an element of the cause of action; to prevail on the merits, every class member must prove at least some antitrust impact resulting from the alleged violation." In re Hydrogen Peroxide Antitrust Litig., 552 F.3d 305, 311 (3rd Cir. 2008). Plaintiffs have alleged harm due to "artificially-inflated" prices for insulin glargine products between February of 2015, when the

[13] In the Amended Complaint, the plaintiffs assert that in the Consent Judgment settling Sanofi I, "Sanofi finally admitted that Lilly's Basaglar did not infringe the vial formulation patents or DCA injector pen patents." Am. Compl. ¶ 242. This allegation is not supported by the record. Rather, the Consent Judgment provides that "by virtue of the license granted by Sanofi to Eli Lilly as part of the Settlement Agreement" Lilly's product does not infringe on the formulation or pen patents. See Sanofi I, Docket No. 279 at 24.

'722 Patent expired, and December 2016, when Lilly was permitted to sell Basaglar pursuant to the Sanofi I settlement.

As explained above, plaintiffs have not pled facts showing that the listing of the '864 patent in the Orange Book was unreasonable, or that the litigation enforcing the '864 patent was a sham. Thus, the '864 patent stood as a lawful bar to Lilly's market entry for as long as it remained in effect, unless otherwise agreed. The '864 patent was set to expire in 2024. Regardless of the anticompetitive harm caused by the formulation and other pen patents on which plaintiffs have sued in the instant case, the '864 patent stood as a lawful bar to entry during the period of alleged harm. This court therefore dismisses those claims as there is no plausible argument for causation.

V. CONCLUSION

For the reasons detailed herein, the Motion to Dismiss (Docket No. 21) is ALLOWED and the Plaintiffs' Amended Class Action Complaint is dismissed without prejudice.

SO ORDERED.

/ s / Judith Gail Dein
Judith Gail Dein
United States Magistrate Judge

UNITED STATES DISTRICT COURT FOR
THE DISTRICT OF MASSACHUSETTS

In re LANTUS DIRECT PURCHASER ANTITRUST LITIGATION	CIVIL ACTION NO. 16-12652-JGD

MEMORANDUM OF DECISION AND ORDER ON DEFENDANT'S MOTION TO DISMISS SECOND AMENDED COMPLAINT

October 24, 2018

DEIN, U.S.M.J.

I. INTRODUCTION

By Memorandum of Decision and Order (Docket No. 40) dated January 10, 2018, this court dismissed the plaintiffs' Amended Complaint without prejudice. Thereafter, plaintiffs were granted leave to and did file a Second Amended Complaint (Docket Nos. 49, 51). Defendant has now moved to dismiss the Second Amended Complaint pursuant to Fed. R. Civ. P. 12(b)(6) (Docket No. 54) (the "Motion to Dismiss"). Plaintiffs have opposed the Motion to Dismiss (Docket No. 59) ("Opp.") and defendant has filed a Reply (Docket No. 62). After oral argument on the Motion to Dismiss, the parties submitted supplemental letters to the court (Docket Nos. 71, 72) addressing questions raised at oral argument. The court has carefully considered the parties' submissions and arguments made in open court. For the reasons detailed herein, the Second Amended Complaint fails to state a claim on which relief can be granted. The Motion to Dismiss is therefore ALLOWED and the Second Amended Complaint is dismissed with prejudice.

II. STATEMENT OF FACTS[1]

Since the Second Amended Complaint is premised on and merely expands upon the allegations of the First Amended Complaint, this court will assume the reader's familiarity with its earlier decision and will not repeat the extensive factual history laid out therein. All of those facts remain relevant to the instant analysis. What follows is a brief overview of the facts and regulatory context for this Motion.

The defendant, Sanofi-Aventis US LLC ("Sanofi"), is a life sciences company that sells, among other medicines, Lantus — an insulin glargine solution used for management of diabetes. See SAC ¶ 3. Lantus is sold in vial form or, as particularly relevant here, in an injector pen known as Lantus SoloSTAR. Id. Plaintiffs, FWK Holdings, LLC and Cesar Castillo, Inc., are purchasers of Lantus and allege that Sanofi unlawfully extended its period of market exclusivity over insulin glargine products and charged supra-competitive prices for Lantus after February 2015. Id. ¶¶ 14, 15, 196, 197. On behalf of themselves and a purported class of similar purchasers, the plaintiffs seek damages for having had to pay those supra-competitive prices. The plaintiffs define the class as anyone who "purchased Lantus (in cartridges or SoloSTAR) directly from Sanofi at any time between February 13, 2015 and December 31, 2016 or until the anticompetitive effects of Sanofi's conduct cease[.]" Id. ¶ 486.

The plaintiffs assert two counts in their Complaint, monopolization and attempted monopolization. Both counts are antitrust claims arising under § 2 of the Sherman Act (15 U.S.C. § 2). Both counts are premised on the plaintiffs' arguments that Sanofi engaged in an

[1] Unless otherwise noted, the facts are derived from the Second Amended Complaint (Docket No. 51) ("SAC").

exclusionary conduct scheme consisting of improperly listing patents in the U.S. Food & Drug Administration's ("FDA") *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book"), commencing and maintaining a sham litigation lawsuit against Eli Lilly & Company ("Lilly"), and engaging in a pattern of anticompetitive serial petitioning. Id. ¶¶ 496-514.

As relevant for this opinion, Sanofi is the holder of "formulation" patents covering preparations of insulin, and "pen" patents covering injector pens or components thereof. Id. ¶¶ 216-217, 249-254, 354, 390-402. As with Sanofi's previous motion to dismiss (Docket No. 21), the instant Motion focuses largely on Sanofi's conduct related to U.S Patent No. 8,556,864 ("the '864 Patent"), titled "Drive Mechanisms Suitable for Use in Drug Delivery Devices." SAC Ex. I. This patent covers a part used in Sanofi's insulin injector pen, the Lantus SoloSTAR. The plaintiffs allege that Sanofi improperly listed the '864 Patent in the Orange Book and commenced sham litigation against Lilly asserting infringement of that patent. Sanofi denies that its conduct related to the '864 Patent was anticompetitive, and argues that because the '864 Patent stood as a lawful bar to competition, the plaintiffs' other allegations fail due to issues of causation.

The Orange Book is intended to put other drug manufacturers on notice of relevant patents. Companies seeking FDA approval of a new drug submit a new drug application ("NDA") pursuant to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et seq.* ("FDCA"). Those companies must list any patents in the Orange Book "which claim[] the drug for which the applicant submitted the application or which claim[] a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted." 21 U.S.C.

§ 355(b)(1). Sanofi submitted an NDA for Lantus and a Supplemental NDA for Lantus SoloSTAR, and has listed patents for each. See SAC ¶¶ 182, 203, 280, 282. The plaintiffs claim that Sanofi improperly listed certain patents, including the '864 Patent, in the Orange Book, thereby illegally gaining the ability to commence litigation against competitors and extend its period of exclusivity, as explained below.

Under the Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984), known as the Hatch-Waxman Amendments, drug manufacturers seeking approval to sell products similar to already approved brand drugs can file an application for approval which relies on a brand manufacturer's NDA. Id. ¶¶ 35, 37, 71. This makes it easier for follow-on or generic manufacturers to gain FDA approval. In doing so, the new manufacturer must certify as to how their product impacts the patents that the brand drug manufacturer listed for its original NDA.

As relevant here, Lilly submitted an application for its insulin glargine product Basaglar, relying on Sanofi's NDA submissions for its Lantus products. Basaglar, like the Lantus SoloSTAR, provides insulin glargine in an injector pen. See id. ¶¶ 300-02. Lilly planned on using its own pen for the product, the KwikPen, which Lilly had previously been using for other products. Id. Because Lilly relied on Sanofi's submissions, it had to file certifications related to Sanofi's patents for Lantus and Lantus SoloSTAR. With the exception of one patent, Lilly certified that Sanofi's listed patents "were invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use, or sale of [Basaglar]." Id. ¶ 306. This type of certification is known as a "paragraph IV certification." Filing a paragraph IV certification "may provoke litigation. The patent statute treats such filing as an act of technical infringement and provides

the brand company an opportunity to sue." Id. ¶ 79; 35 U.S.C. § 271(e)(2)(A). Thus, if Sanofi had reason to believe that Lilly's product infringed any of its listed patents when Lilly filed its paragraph IV certification, it had the opportunity to sue Lilly prior to the FDA approving Lilly's product. "If the branded drug manufacturer initiates a patent infringement action against its would-be competitor within forty-five days of receiving notification of the paragraph IV certification, the FDA will not grant final approval to the [new drug application] until the earlier of (a) the passage of 30 months, or (b) the issuance of a decision by a court that the patent is invalid or not infringed by the [new] product." Id. ¶ 80; 21 U.S.C. § 355(c)(3)(C).

After receiving Lilly's paragraph IV certifications, Sanofi sued Lilly for patent infringement on two of the formulation patents and two of the pen patents, including the '864 patent. SAC ¶ 325. The plaintiffs claim that this litigation was a sham because it was based on improper Orange Book listings and because Sanofi had no reasonable basis for thinking that its patents were infringed. As is provided for by 21 U.S.C. § 355(c)(3)(C), the lawsuit against Lilly triggered an automatic stay of FDA approval for Basaglar. Id. ¶ 326. On September 28, 2015, the morning of trial, Lilly and Sanofi settled the litigation. Id. ¶ 375. As part of the settlement, Sanofi granted Lilly a royalty-bearing license so that Lilly could manufacture and sell Basaglar, and Lilly agreed to delay its launch of Basaglar until December 15, 2016. Id. ¶¶ 375-77.

In addition to the conduct related to Lilly, the plaintiffs include in their Second Amended Complaint additional facts that they claim add to Sanofi's overall anticompetitive scheme. First, the plaintiffs allege that "[e]ven after Sanofi's litigation with Lilly, [Sanofi] expected other companies would soon seek to create affordable follow-on insulin glargine products. To further frustrate those efforts, Sanofi obtained and then listed in the Orange Book an additional

thirteen patents over its SoloSTAR injector pen." Id. ¶ 389 (emphasis omitted). The plaintiffs allege that "[n]one of the new patents claim insulin or insulin glargine. Each claims one or more aspects of the SoloSTAR packaging. All are improperly listed in the Orange Book and serve to frustrate competition." Id. ¶ 403. Second, the plaintiffs allege that Sanofi commenced lawsuits against would-be competitors Merck and Mylan, exhibiting a "pattern of anticompetitive petitioning for which [Sanofi] is independently liable under federal antitrust law, even if each act of petitioning is not independently objectively baseless." Id. ¶ 500.

This court granted Sanofi's first motion to dismiss on January 10, 2018 (Docket No. 40). Therein, this court held that the plaintiffs failed to state a claim related to antitrust liability stemming from improper Orange Book listings because the alleged facts did not show that it was unreasonable to list the '864 Patent. This court also dismissed the plaintiffs' sham litigation claim, ruling that the plaintiffs failed to plead facts which showed that Sanofi's litigation against Lilly involving the '864 Patent was objectively baseless. As the '864 Patent stood as a legal barrier to Basaglar's market entry prior to December 15, 2016, this court dismissed the plaintiffs' remaining allegations for lack of causation. The court's dismissal was without prejudice. The plaintiffs have now submitted a Second Amended Complaint and Sanofi has again moved for this court to dismiss both counts.

Additional facts are included herein as necessary.

III. LEGAL STANDARD

A. Motion to Dismiss for Failure to State a Claim

While Sanofi has moved to dismiss the Second Amended Complaint for failure to state a claim pursuant to Federal Rule of Civil Procedure 12(b)(6), it argues further that this court

should decline to reconsider its earlier rulings, and, instead, invoke the "law of the case" doctrine. See Mem. in Supp. of Motion to Dismiss (Docket No. 55) at 13-14. The law of the case doctrine holds that "unless corrected by an appellate tribunal, a legal decision made at one stage of a civil or criminal case constitutes the law of the case throughout the pendency of the litigation." Ellis v. United States, 313 F.3d 636, 646 (1st Cir. 2002) (internal citation and quotation omitted). In light of the substantial new allegations of the Second Amended Complaint, however, as well as the extensive arguments presented by the parties, this court has considered the sufficiency of the Second Amended Complaint anew, and applied the 12(b)(6) standard of review. Nevertheless, as detailed below, this court has not altered its decision and incorporates herein the analysis included in its decision of January 10, 2018 (Docket No. 40) (hereinafter, "Order").

Standard of Review

Motions to dismiss under Rule 12(b)(6) test the sufficiency of the pleadings. When confronted with such a motion, the court accepts as true all well-pleaded facts and draws all reasonable inferences in favor of the plaintiff. See Cooperman v. Individual Inc., 171 F.3d 43, 46 (1st Cir. 1999). The court may also consider "implications from documents attached to or fairly incorporated into the complaint . . . facts susceptible to judicial notice . . . [and] concessions in plaintiff's response to the motion to dismiss." Schatz v. Republican State Leadership Comm., 669 F.3d 50, 55-56 (1st Cir. 2012) (internal quotations and citations omitted).

As the First Circuit has explained, in considering the merits of a motion to dismiss, the court proceeds in two steps. First, we "isolate and ignore statements in the complaint that simply offer legal labels and conclusions or merely rehash cause-of-action elements." Id. at 55.

Second, we "take the complaint's well-pled (*i.e.*, non-conclusory, non-speculative) facts as true, drawing all reasonable inferences in the pleader's favor, and see if they plausibly narrate a claim for relief." Id. Dismissal is only appropriate if the complaint, so viewed, fails to allege "a plausible entitlement to relief." Rodriguez-Ortiz v. Margo Caribe, Inc., 490 F.3d 92, 95 (1st Cir. 2007) (quoting Bell Atl. Corp. v. Twombly, 550 U.S. 544, 559, 127 S. Ct. 1955, 1967, 167 L. Ed. 2d 929 (2007)). "Plausible . . . means something more than merely possible[.]" Schatz, 669 F.3d at 55. "The bottom line is that the combined allegations, taken as true, must state a plausible, not merely conceivable, case for relief." Carrero-Ojeda v. Autoridad de Energia Electrica, 755 F.3d 711, 718 (1st Cir. 2014) (internal citations and quotations omitted). "Engaging in this plausibility inquiry is 'a context-specific task that requires the reviewing court to draw on its judicial experience and common sense.'" Germanowski v. Harris, 854 F.3d 68, 72 (1st Cir. 2017) (quoting Ashcroft v. Iqbal, 556 U.S. 662, 679, 129 S. Ct. 1937, 1950, 173 L. Ed. 2d 868 (2009)).

B. Monopolization and Attempted Monopolization Under the Sherman Act

Plaintiffs bring two counts under the Sherman Act, 15 U.S.C. § 2, one for monopolization and the other for attempted monopolization. SAC ¶¶ 496-514. In order to be successful on a claim under § 2 of the Sherman Act, a plaintiff must "demonstrate (1) that the defendant possesses monopoly power in the relevant market, and (2) that the defendant has acquired or maintained that power by improper means." Town of Concord v. Boston Edison Co., 915 F.2d 17, 21 (1st Cir. 1990) (internal quotations and citations omitted). "[A] practice, a method, a means, is 'improper' if it is 'exclusionary.' To decide whether [a company's] conduct was exclusionary, we should ask whether its dealings with [a competitor] went beyond the needs of ordinary business dealings, beyond the ambit of ordinary business skill, and 'unnecessarily

excluded competition' from the [] market." Barry Wright Corp. v. ITT Grinnell Corp., 724 F.2d 227, 230 (1st Cir. 1983) (internal citations omitted). Thus, successful claims of monopolization must establish "that the defendant 'has engaged in impermissible 'exclusionary' practices with the design or effect of protecting or enhancing its monopoly position.'" Boston Sci. Corp. v. Schneider (Europe) AG, 983 F. Supp. 245, 268 (D. Mass. 1997) (quoting Coastal Fuels of P.R., Inc. v. Caribbean Petroleum Corp., 79 F.3d 182, 195-96 (1st Cir. 1996)). "In other words, the acquisition and maintenance of the power must be willful, rather than a result of legitimate means such as patents, superior products, business acumen, or historic accident." Id. Finally, "[a]ttempted monopolization under § 2 of the Sherman Act requires proof of (1) anti-competitive or exclusionary conduct; (2) specific intent to monopolize; and (3) a dangerous probability that the attempt will succeed." Id., and cases cited.

Applying these principles compels the conclusion that Sanofi's Motion to Dismiss must be allowed.

IV. ANALYSIS

A. Orange Book Listing

The plaintiffs ask this court to reconsider its prior holding that the Complaint fails to state a claim that Sanofi had unreasonably listed the '864 Patent in the Orange Book. In particular, the plaintiffs continue to assert that the '864 Patent is just for packaging, and that it was improper to list it in the Orange Book since the Patent does not claim the approved drug product. See, e.g., Opp. at 19-24. Sanofi, on the other hand, continues to argue that the '864 Patent was appropriately listed as a "drug delivery system[ ] used and approved in combination with a drug." Reply at 4. This court previously held that "while it may be debatable whether

the Lantus SoloSTAR fits neatly into the category of patents that must be disclosed, it does not fit into the category of patents that must not be disclosed." Order at 21. The allegations in the Second Amended Complaint do not warrant a different conclusion. The court once again concludes that the facts in the Second Amended Complaint are insufficient to show that Sanofi unreasonably or improperly listed the '864 Patent in the Orange Book.

Appropriate Standard of Review

As addressed in this court's prior Order, "Orange Book listing is a statutory obligation and enforcement is a statutory right." In re Lipitor Antitrust Litig., No. 12-2389, 2013 WL 4780496, at *21 (D.N.J. Sept. 5, 2013); see also In re Solodyn (Minocycline Hydrochloride) Antitrust Litig., No. 14-02503, 2015 WL 5458570, at *12 (D. Mass. Sept. 16, 2015). Applicants are "required by law" to identify "any patent that 'claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug.'" In re Buspirone Patent Litig., 185 F. Supp. 2d 363, 371 (S.D.N.Y. 2002) (quoting 21 U.S.C. § 355(b)(1)).

While companies must list certain patents in the Orange Book, improperly listing a patent may subject the patent holder to antitrust liability. See id. at 373 (conduct in providing information for listing in Orange Book is "not immune from liability under the Sherman Act."). Importantly, however, an improper listing does not give automatic rise to antitrust liability. This court established in its prior Order, and reaffirms here, that in order to establish a claim under the Sherman Act for Orange Book listing, a party must show that the defendant's decision to list a patent was unreasonable. See Order at 19.

The plaintiffs contend that this court was incorrect in using such a reasonableness standard. They argue that the court improperly focused on whether Sanofi reasonably (or unreasonably) believed that the '864 Patent fit within the criteria for patents to be listed in the Orange Book. See Opp. at 24-26. This misconstrues this court's ruling. Sanofi's subjective belief as to the propriety of its interpretation of the listing requirements is not at issue. Rather, as this court previously ruled, and confirms herein, it is objectively reasonable to interpret the Listing Provisions in 21 C.F.R. § 314.53 and the associated FDA Response as allowing the '864 Patent to be listed in the Orange Book as a component of a drug delivery system. Therefore, in listing the '864 Patent, Sanofi did not engage in improper conduct. See Organon, Inc. v. Mylan Pharm., Inc., 293 F. Supp. 2d 453, 460 (D.N.J. 2003) ("given the statutory and regulatory language at the time it submitted the '099 Patent for listing in the Orange Book, Organon had a reasonable basis for the submission, and therefore, Organon's listing was not improper."). While the plaintiffs attempt to distinguish Organon on the grounds that the regulatory language at issue in that case was ambiguous and the Orange Book listing requirements here are not, that attempt must fail. As detailed in this court's prior Order and herein, the listing requirements and associated guidance are subject to differing interpretations. Where there is more than one reasonable interpretation of the listing requirements, and a party follows one of those interpretations, the conduct is not improper.

The '864 Patent is Not Just for Packaging

The plaintiffs argue that the '864 Patent is for packaging and is precluded from being listed in the Orange Book. This court found that argument unpersuasive in its earlier decision. See Order at 20. While the plaintiffs have expanded on their legal arguments in their Second

Amended Complaint, they have not added any substantive facts which compel this court to reach a different result.

As an initial matter, the plaintiffs contend that the Lantus SoloSTAR was approved only as packaging. This contention is belied by the record. Rather, the SoloSTAR was approved as a drug product.

It is undisputed that Lantus SoloSTAR is sold as an injector pen filled with insulin glargine. See SAC ¶ 209. Lantus SoloSTAR was approved as a "disposable insulin injection device." SAC Ex. D. The 2003 Comments and Response from the FDA, discussed in detail in this court's prior Order, indicate that "pre-filled drug delivery systems" are drug products for Orange Book listing purposes. See Order at 7-9 (discussing 68 Fed. Reg. 36676-01, 2003 WL 21391636, at 36,680 (June 18, 2003) ("FDA Response")). As evidenced by the FDA website, of which this court takes judicial notice, insulin injector pens are considered "pre-filled drug delivery systems." FDA, https://www.fda.gov/CombinationProducts/AboutCombination Products/ucm101496.htm#examples (last visited Oct. 22, 2018) (listing as examples of combination products "[p]refilled drug delivery systems (syringes, insulin injector pen, metered dose inhaler)"); see Kader v. Sarepta Therapeutics, Inc., No. 14-14318, 2016 WL 1337256, at *11 (D. Mass. Apr. 5, 2016) (holding that official statements of the FDA made on a government website constitute public records of which the court can take judicial notice). The FDA's SoloSTAR approval letter refers to the Lantus SoloSTAR as a "drug product." SAC Ex. D. ("If you issue a letter communicating important information about this drug product . . . we request that . . . .").

In an effort to avoid this conclusion, the plaintiffs excerpt various phrases from communications between the FDA and Sanofi relating to the proposed labelling for the SoloSTAR in which "the FDA repeatedly referred to the [SoloSTAR] pen as a container" or "packaging." SAC ¶¶ 203-10. The plaintiffs rely on these select comments in concluding that "it was unreasonable for Sanofi to believe that its [supplemental new drug application] approval was for anything other than a package change." Id. ¶ 211. However, these select references must be placed in context. As Sanofi accurately asserts, "[t]hose references concerned where to put the drug label in order to minimize the risk of medication errors and how to protect the insulin cartridge integrated into the device." Reply at 4-5 (citing SAC Ex. N at 68-78, 98-101). A fair reading of the referenced communications shows that the FDA approved SoloSTAR as a "disposable insulin injection device." SAC Ex. D; Cf. SAC ¶ 204. It is consistently referred to by the FDA as a "device." See SAC Ex. N at 68, 71, 74, 76. The record compels the conclusion, as detailed in this court's earlier Order, that the SoloSTAR was not just packaging but was approved as a drug delivery system. Order at 20-21.

Need to Claim the Drug Product

As before, the plaintiffs next allege that Sanofi was unreasonable in listing the '864 Patent because it does not claim the relevant drug or drug product. They assert that it was improper to list the '864 Patent, which claims only components of an injector pen but does not mention Lantus SoloSTAR, or insulin glargine, because the Regulations provide that "[f]or patents that claim a drug product, the applicant must submit information only on those **patents that claim the drug product**, as defined in § 314.3, that is described in the pending or approved NDA." 21 C.F.R. § 314.53(b)(1) (emphasis added). The plaintiffs argue that since the '864

Patent does not expressly mention Lantus, Lantus SoloSTAR, or insulin glargine, it is improper to list it in the Orange Book as claiming Lantus SoloSTAR. This court does not agree.

As detailed in this court's earlier Order, the FDA's guidance regarding what a patent must expressly claim is ambiguous and is reasonably read to allow for the listing of the '864 Patent. The FDA has expressly interpreted "drug products", for which patents must be listed in the Orange Book, to include "pre-filled drug delivery systems." See FDA Response. Similarly, as detailed above, the FDA has recognized that insulin injector pens constitute "pre-filled drug delivery systems" and it approved SoloSTAR as a "disposable insulin injection device." Hence, it is reasonable to interpret the FDA Regulations as requiring the listing of patents for devices such as SoloSTAR regardless of whether the patent itself expressly references insulin glargine, or insulin glargine in conjunction with the pen-type injector. See SAC ¶ 272.

This court previously held on this point that "even assuming such a 'claim' must be made in the patent, it is not clear whether or not the 'claims' of the '864 patent, which are for a drug delivery device which includes a dose dial sleeve and a dose limiting mechanism, among other things, are sufficient to satisfy any such requirement." Order at 21. The court hereby affirms its prior ruling. The '864 Patent indisputably claims components of the Lantus SoloSTAR, which, as addressed *supra*, Sanofi correctly had reason to believe met the definition of "drug product" under the ambiguous FDA guidance. The plaintiffs have not alleged facts which show that it was unreasonable for Sanofi to list patents claiming components of that drug product.

The plaintiffs rely on Pfizer, Inc. v. FDA, 753 F. Supp. 171 (D. Md. 1990), to argue that patents for components of a drug product should not be listed. Opp. at 17-18. The court in

Pfizer, however, did not hold that component parts of drugs cannot be listed — rather, the court ruled that listed components must be part of the specific drug "for which the applicant submitted the application." 753 F. Supp. at 176-77.

The listed drug at issue in Pfizer was a "nifedipine solution in a soft gelatin capsule, which Pfizer markets in the United States under the trade name Procardia." Id. at 173. The FDA in that case refused to list Pfizer's '986 patent, "which claimed a tablet formulation of nifedipine[,]" in the Orange Book for Procardia. Id. at 174. The FDA had two principal issues with listing the '986 patent. First, the FDA needed proof that the composition underlying the tablet formulation in the '986 patent was approved. Id. Second, the FDA relied on its own interpretation of the term "drug" to conclude that patents need only be filed when they claim the listed drug or drug product for which the NDA was submitted. Id. at 174-75. While both Procardia, a soft gelatin capsule, and Pfizer's tablet formulation include nifedipine, they were two distinct products. See id. at 176. The court in Pfizer held that a listed patent must claim the approved drug product for which the NDA was submitted – in that case Procardia. Id. Pfizer could not submit a patent for a different product just because it shared an active ingredient with Procardia. Pfizer was not submitting components of Procardia itself, but a patent for a different product which shared a component with Procardia.[2] In the instant case, by comparison, Sanofi's patent listed a component of Lantus SoloSTAR, the relevant approved drug product. Including the '864 Patent in the Orange Book is entirely consistent with Pfizer.

[2] The Pfizer court's discussion of the definition of "drug" recognized that it includes component parts of the final drug. Id. at 176 (citing 21 U.S.C. § 321(g)(1)); see also United States v. Generix Drug Corp., 460 U.S. 453, 459, 103 S. Ct. 1298, 1301-02, 75 L. Ed. 2d 198 (1983) ("The term 'drug' is plainly intended throughout the Act to include entire drug products, complete with active and inactive ingredients."). Recognizing component parts of a drug product is entirely consistent.

Finally, the plaintiffs disagree with this court's interpretation of correspondence between companies and the FDA, which evidence confusion in the industry over the very question presented by this litigation. See, e.g., Letter from GSK to FDA, Docket No. FDA-2005-A-0476 (Feb. 11, 2009), available at https://www.regulations.gov/document?D=FDA-2005-A-0476-0004 ("in the absence of further guidance from the FDA, [GSK] has modified its Orange Book listing practice to list those patents . . . that claim all or a portion of integrated drug-device products, regardless of whether the approved drug substance is specifically mentioned in the claims of such patents."). This court also took judicial notice of responses from the FDA, including a 2011 response to an inquiry from Forest Laboratories, Inc., in which the FDA wrote that "due to the need to address other Agency priorities," it "has been unable to reach a decision" on "whether a patent that claims a drug delivery device whose use is integral to the administration of the active ingredient and the approval of the NDA, but that does not claim the active ingredient of the approved drug product, should be submitted for listing in [the Orange Book]." Interim Response to Forest Laboratories, Inc., Docket No. FDA-2011-A-0363 (Nov. 7, 2011), available at https://www.regulations.gov/document?D=FDA-2011-A-0363-0008.

The plaintiffs claim that the letters show, not confusion, but rather an admission by industry members that the current framework does not allow for the listing of patents unless that patent explicitly claims the active drug substance. The court takes judicial notice of the letters themselves, and is not bound to accept the interpretation of their content provided by either party. See OrbusNeich Med. Co. v. Boston Sci. Corp., 694 F. Supp. 2d 106, 111 (D. Mass. 2010) ("The public filing of [a] document with a regulatory agency [] makes it a proper subject of judicial notice, at least with regard to the fact that it contains certain information, though not

as to the truth of its contents."). The letters, posing the question of whether component patents must be listed, further show what this court has held – that the ambiguous listing requirements in this area allow for Sanofi's interpretation permitting the listing of the '864 Patent.

For the foregoing reasons, the plaintiffs again fail to state a claim for Sherman Act violations based on the Orange Book listing of the '864 Patent.

B. Litigation Against Lilly

The plaintiffs also ask this court to reconsider its prior order dismissing their sham litigation claim. They contend that Sanofi engaged in exclusionary conduct through "[c]ommencing and maintaining a sham litigation against Lilly to delay introduction of competing insulin glargine products into the U.S. market." SAC ¶ 498. The plaintiffs further claim that "Sanofi's suit against Lilly was objectively baseless and motivated by a subjective desire to delay competition in the insulin glargine market." Id. ¶ 499. This court previously dismissed the plaintiffs' sham litigation claim regarding the Lilly lawsuit. The allegations in the Second Amended Complaint do not compel a different result.

Once Lilly filed its paragraph IV certification, Sanofi had the statutory right to sue under 35 U.S.C. § 271(e)(2)(A). A paragraph IV certification is deemed to be "a defined act of infringement sufficient to create case or controversy jurisdiction to enable a court to promptly resolve any dispute concerning infringement and validity." Glaxo, Inc. v. Novopharm, Ltd., 110 F.3d 1562, 1569 (Fed. Cir. 1997). Importantly, while a patent holder has the right to sue upon receipt of a paragraph IV certification, it is not obligated to do so.

The filing of a lawsuit is generally protected activity under the First Amendment, as recognized by the Noerr-Pennington doctrine. E. R.R. Presidents Conference v. Noerr Motor Freight, Inc., 365 U.S. 127, 81 S. Ct. 523, 5 L. Ed. 2d 464 (1961); and United Mine Workers of Am. v. Pennington, 381 U.S. 657, 85 S. Ct. 1585, 14 L. Ed. 2d 626 (1965). However, this immunity is lost if the lawsuit is a "sham." See In re Solodyn (Minocycline Hydrochloride) Antitrust Litig., No. 14-02503, 2015 WL 5458570, at *11 ("Under the Noerr-Pennington doctrine, filing a lawsuit is protected under the First Amendment unless the lawsuit is a 'sham.'" (citing Prof'l Real Estate Investors, Inc. v. Columbia Pictures Indus., Inc., 508 U.S. 49, 60-61, 113 S. Ct. 1920, 1928, 123 L. Ed. 2d 611 (1993))).

The Supreme Court has identified a two-part definition for sham litigation.

> First, the lawsuit must be objectively baseless in the sense that no reasonable litigant could realistically expect success on the merits. If an objective litigant could conclude that the suit is reasonably calculated to elicit a favorable outcome, the suit is immunized under Noerr, and an antitrust claim premised on the sham exception must fail. Only if challenged litigation is objectively meritless may a court examine the litigant's subjective motivation. Under this second part of our definition of sham, the court should focus on whether the baseless lawsuit conceals an attempt to interfere directly with the business relationships of a competitor ....

Prof'l Real Estate Investors, Inc., 508 U.S. at 60-61, 113 S. Ct. at 1928 (internal quotations, citations, and emphasis omitted). To prevail, "a plaintiff must allege that both prongs of the test are met." United Food & Commercial Workers v. Novartis Pharm. Corp., 902 F.3d 1, 13 (1st Cir. 2018). In the instant case, Sanofi contends that the plaintiffs have failed to allege that its litigation to enforce the '864 Patent was "objectively baseless." See, e.g., id.; see also 800 Adept, Inc. v. Murex Sec., Ltd., 539 F.3d 1354, 1370 (Fed. Cir. 2008) (to prove objectively baseless prong, the plaintiff had to prove the defendant "had no reasonable basis to believe

that its patent claims were valid or that they were infringed[.]"). This court agrees, and concludes that the plaintiffs have not alleged sufficient facts to make the necessary showing.

Plaintiffs argue that they have cured deficiencies from their previous complaint related to the Lilly sham litigation claim. Opp. at 28-31. The court disagrees. This court found the following in its prior Order:

> According to the Amended Complaint, prior to bringing suit Sanofi had the pages of Lilly's § 505(b)(2) application that (1) showed the list of ingredients of Lilly's NDA product, and (2) identified the type of injector pen by which the Lilly NDA product would be administered. Other than repeatedly stating that the documents showed that Lilly's products would not infringe any of the claims in the two injector pen patents (the '864 and '044 patents) or any claims in the two vial formulation patents (the '652 and '930 patents), the plaintiffs have offered no facts in support of these conclusions. Since this court must disregard conclusory allegations of fact and law, the allegations of the Amended Complaint are insufficient to show that the underlying lawsuit lacked any reasonable merit.

Order at 27 (internal citations and quotations omitted). This court also found that other factors supported the conclusion that the underlying lawsuit was not objectively baseless, including the fact that Sanofi was enforcing valid patents in the face of a paragraph IV certification, that the litigation was hard fought on issues related to the '864 Patent, and that the settlement included favorable terms to Sanofi.

The plaintiffs have amended their Complaint to include facts they believe are sufficient to show that Sanofi's lawsuit against Lilly lacked any reasonable merit. First, the plaintiffs allege in detail the differences between the two pens. SAC ¶¶ 333-343. They assert that, based on those differences, "[n]o reasonable pharmaceutical company in Sanofi's position would realistically expect to succeed in proving infringement." Id. ¶ 332. Next, the plaintiffs assert that if there was a valid basis for infringement, Sanofi would have sued Lilly earlier, when Lilly

used its KwikPen in connection with another insulin product Humalog. Id. ¶¶ 289-298. The plaintiffs contend that since "Sanofi never took the position that Lilly's KwikPen infringed Sanofi's initial injector pen patents, let alone sue Lilly for infringement[,]" Sanofi had no reasonable basis to claim that the KwikPen infringed Sanofi's patents in connection with Lantus or Lantus SoloSTAR. Id. ¶ 298. Finally, the plaintiffs allege that when Sanofi launched a follow-on version of Lilly's Humalog product using its SoloSTAR pen, Sanofi filed a paragraph IV certification alleging that "Lilly's '132 patent was 'invalid, unenforceable, or will not be infringed' by Sanofi's Admelog SoloSTAR product." Id. ¶ 438. The plaintiffs allege that Sanofi's paragraph IV certification in that instance contradicts its position in the Lilly litigation that Basaglar infringed the '864 Patent. See id.

Even considering these new allegations, however, the plaintiffs have failed to allege sufficient facts to establish that Sanofi's suit against Lilly ("Sanofi I") was objectively baseless. "A firm that has received a patent from the patent office (and not by fraud . . .), and thus enjoys the presumption of validity that attaches to an issued patent . . . is entitled to defend the patent's validity in court, to sue alleged infringers, and to settle with them, whatever its private doubts, unless a neutral observer would reasonably think either that the patent was almost certain to be declared invalid, or the defendants were almost certain to be found not to have infringed it, if the suit went to judgment." United Food & Commercial Workers Unions v. Novartis Pharm. Corp., No. 15-12732, 2017 WL 2837002, at *11 (D. Mass. June 30, 2017) (internal quotation and citation omitted), aff'd, 902 F.3d 1 (1st Cir. 2018). It does not matter whether Sanofi would have prevailed at trial. If Sanofi had even a colorable claim of infringement, it is afforded Noerr-Pennington immunity. Id.; see also Asahi Glass Co. v. Pentech

Pharm., Inc., 289 F. Supp. 2d 986, 995 (N.D. Ill. 2003) ("to avoid turning every patent case into an antitrust case, some threshold of plausibility must be crossed at the outset before a patent antitrust case should be permitted to go into its inevitably costly and protracted discovery phase . . . the determination of whether such a suit is a sham depends not on what the patentee believes but on the nature of and the underlying merits of the patentee's case." (internal citations and quotations omitted)). Thus, even if the plaintiffs are right that Lilly would have ultimately prevailed at trial, that is not the question before the court. The sham litigation exception to the Noerr-Pennington doctrine was not intended to provide all third parties with an opportunity to re-litigate cases. The doctrine was reserved for those cases in which the record shows that the suit was objectively baseless.

None of the plaintiffs' new allegations show that Sanofi's suit was objectively baseless. While the plaintiffs now provide the court with ample allegations showing the differences between the injector pens, these differences do not objectively show that Lilly's product did not infringe Sanofi's '864 Patent. Despite the alleged differences between the pens, the underlying litigation docket shows a hard fought case in which non-infringement was anything but clear.[3] See AstraZeneca AB v. Mylan Labs., Inc., Nos. 00-6749, 03-6057, 2010 WL 2079722, at *4 (S.D.N.Y. May 19, 2010) (finding that the underlying lawsuit was "hard-fought and close" and that such an "outcome hardly bespeaks baseless litigation."). For example, the record in Sanofi I is clear that Sanofi was asserting that Lilly's pen violated the claims in the '864 Patent. See Sanofi I Joint Claim Construction Brief (Docket No. 149) at 1. Sanofi's contention that the

[3] The court takes judicial notice of the underlying litigation. Maher v. Hyde, 272 F.3d 83, 86 n.3 (1st Cir. 2001) (holding that a court may take judicial notice of the docket of any court case).

'864 Patent had been infringed formed the basis of many of Sanofi's discovery requests. See, e.g., Sanofi I Docket No. 224 at 1 ("Lilly's accused product includes a pen containing various components that, when assembled, combine to form a closing mechanism. Sanofi's asserted device patents include claims to injection devices having particular components, and Sanofi must therefore be able to analyze the structure of the internal components of Lilly's accused device."); see also Docket Nos. 215, 227 (discovery letters).

The court in Sanofi I conducted an extensive claims construction process in which the court accepted some of each party's constructions of the '864 Patent. Sanofi I Docket No. 192. The extent of the litigation negates the plaintiffs' assertion that no reasonable pharmaceutical company would expect to succeed on infringement claims. The fact that the pens had many differences does not show otherwise.

The plaintiffs' allegations regarding Sanofi's conduct related to another insulin product Humalog are also unsuccessful in showing that the underlying suit was baseless. Sanofi's decision not to sue Lilly previously, and decision to file a paragraph IV certification with regard to another drug product, do not show that Sanofi's belief in this particular instance was baseless. Those allegations, even if true, do not show that Sanofi had no reasonable expectation of winning its suit against Lilly concerning this product, Basaglar.[4]

Finally, the settlement between Sanofi and Lilly in the underlying lawsuit provides further support for the conclusion that the lawsuit was not baseless. See Toyo Tire & Rubber

[4] This conclusion is supported by the fact that these facts were all known at the time of Sanofi I and Lilly raised some of the same arguments yet nevertheless proceeded towards trial and eventual settlement in Sanofi I. See Sanofi I Docket No. 149 at 3 ("the injector pen part patents were never asserted against Lilly's marketed KwikPen product.").

Co., Ltd. v. Atturo Tire Corp., No. 14-0206, 2017 WL 1178224, at *4 (N.D. Ill. Mar. 30, 2017) ("courts have invariably held that lawsuits terminating in favorable settlement are also objectively reasonable and are not shams"). Under the terms of the settlement, Lilly was granted a royalty-bearing license such that Lilly could manufacture and sell Basaglar in the KwikPen device globally. SAC ¶ 375. Sanofi, for its part, gained royalties and a delay in Lilly coming to market. Lilly gained the ability to come to market before the expiration of the patents at issue, including the '864 Patent. See id. The court is certainly aware that "[p]arties may settle a litigation for a variety of reasons independent of the merits of the claims." Morton Grove Pharm. Inc. v. Par Pharm. Co., No. 04-7007, 2006 WL 850873, at *11 (N.D. Ill. Mar. 28, 2006) (internal citations omitted). This court acknowledges both parties' arguments related to the import of the settlement, and simply notes that the existence of such a settlement supports the conclusion that Sanofi's underlying infringement claim was at least colorable. For the foregoing reasons, the plaintiffs have failed to state a claim for antitrust violations related to sham litigation.

C. Serial Petitioning

The court must next address the plaintiffs' added allegations related to serial petitioning. The plaintiffs argue that Sanofi has filed two additional lawsuits against Merck and Mylan, which, when assessed in connection with the Lilly lawsuit, constitute a "pattern of anticompetitive petitioning for which [Sanofi] is independently liable under federal antitrust law, even if each act of petitioning is not independently objectively baseless."[5] SAC ¶ 500. The plaintiffs

[5] The lawsuit with Merck is Sanofi-Aventis U.S. LLC v. Merck Sharp & Dohme Corp., No. 16-00812 (D. Del. filed Sept. 16, 2016). The parties completed a five day bench trial on June 4, 2018 and have

allege that "[s]imply by filing those suits (which were just as meritless as Sanofi's suit against Lilly), Sanofi triggered regulatory stays that [are] delaying full competition in the Lantus and insulin glargine market lasting at least into 2020." Id. ¶ 11. The plaintiffs claim this is particularly harmful to purchasers because, even though Lilly's product is now on the market, "the largest drop in product price occurs when the number of follow-on products in the market goes from one to two[.]" Id. ¶ 424.

As relevant to the Merck lawsuit, Merck submitted an application for its version of insulin glargine on May 31, 2016. Id. ¶ 405. Merck "included a paragraph IV certification to the laundry list of patents then listed in the Orange Book as covering Lantus and Lantus SoloSTAR, on August 4, 2016." Id. ¶ 407. The plaintiffs allege that Sanofi "refused to accept or review portions of Merck's NDA to determine if it had a viable, non-frivolous claim of patent infringement." Id. ¶ 410. "Instead, on September 16, 2016, Sanofi sued Merck on [] ten patents in the United States District Court for the District of Delaware." Id. ¶ 411.

The second lawsuit the plaintiffs rely on is against Mylan. The plaintiffs allege that "rather than wait for Sanofi to sue Mylan and block competition, Mylan brought the fight to Sanofi[.]" Id. ¶ 426. "On June 5, 2017, Mylan filed with the Patent Trials and Appeals Board ("PTAB") petitions for inter partes review [ ] of Sanofi's vial formulation patents – the '652 patent and the '930 patent." Id. ¶ 427. The plaintiffs assert that "Sanofi opposed the petitions, but on December 13, 2017, the PTAB granted Mylan's petitions – meaning Mylan had demonstrated a 'reasonable likelihood of success' in showing at least one claim of each patent

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submitted post trial briefing. The lawsuit with Mylan is Sanofi-Aventis U.S. LLC v. Mylan N.V., No. 17-09105 (D.N.J. filed Oct. 24, 2017). The litigation is ongoing.

would be found invalid – and instituted an inter partes review of the vial formulation patents." Id. ¶ 428 (internal punctuation omitted). Mylan separately filed an application "seeking permission to manufacture, market, and sell a follow-on version of Lantus SoloSTAR. Contained within its application was a paragraph IV certification that the plethora of vial formulation patents and injector pen patents listed under Lantus in the Orange Book were invalid, unenforceable, or would not be infringed by Mylan's proposed follow-on insulin glargine product." Id. ¶ 430. As with Merck, the plaintiffs claim that Sanofi "refused to accept or review portions of Mylan's NDA to determine whether it had any viable, non-frivolous claim of infringement against Mylan." Id. ¶ 433. "Sanofi sued Mylan on October 24, 2017, alleging that Mylan infringed every one of Sanofi's eighteen injector pen patents and vial formulation patents." Id. ¶ 434. As a result of the lawsuit, "the FDA was automatically prohibited from approving Mylan's product for 30 months, or until March 18, 2020." Id. ¶ 435.

The plaintiffs allege that these two lawsuits, which were filed in response to paragraph IV certifications, subject Sanofi to antitrust liability regardless of their merit. The court does not agree. In its recent decision affirming summary judgment for a competitor in the face of allegations of serial petitioning, the First Circuit noted that although not every suit need be baseless in order for a serial petitioning claim to survive, "the task here is to identify sham litigation, not probable winners. And while we can see the logic inherent in reasoning that a nonfrivolous suit might be viewed differently when flown in a flock of frivolous suits, we see little logic in concluding that an exercise of the right to file an objectively reasonable petition loses its protection merely because it is accompanied by other exercises of that right." P.R. Tel. Co. v. San Juan Cable LLC, 874 F.3d 767, 772 (1st Cir. 2017). In concurring, Judge Barron, joined by Judge

Torruella, explained that in evaluating serial petitioning cases, the court relies "on a more record-based, case-specific line of reasoning that . . . leaves open the possibility that . . . a monopolist might be liable under the antitrust laws for engaging in a pattern of petitioning, even though no single filing in that pattern is objectively baseless." Id. at 773. Judge Barron explained further that "[t]he antitrust violation – if it exists – in a pattern case of that kind inheres in the monopolist's use of the petitioning process to make the costs of the rival's petitioning activity so high that the rival cannot secure the legal relief that would enable it actually to become a competitor." Id. at 776. Judge Barron noted that "no circuit has actually permitted a suit to go forward in which the underlying petitions were not baseless and there was no clear and convincing evidence that an alleged monopolist sought to use the govern-mental process [] as an anticompetitive weapon." Id. at 777 (citations, quotations, and emphasis omitted). The court does not find, in the allegations of the Second Amended Complaint, facts related to these three lawsuits to meet the high bar necessary for the plaintiffs to make a plausible serial petitioning claim. Each suit followed a paragraph IV certification, an act of infringement that permits a company to sue on a colorable claim. Sanofi contends that it did not fully review the records before engaging in litigation in part because Merck and Mylan demanded burdensome confidentiality agreements. Reply at 14. Even if Sanofi did not fully review Merck and Mylan's applications, and even if the PTAB made a preliminary ruling in Mylan's favor, Sanofi has a protective right to sue and defend colorable claims related to its listed patents. The plaintiffs have neither pleaded a plausible case that these suits were individually baseless, nor have they pleaded a plausible case that Sanofi, through filing these

lawsuits, used the governmental process as an anticompetitive weapon. The plaintiffs' antitrust claims, as premised on serial petitioning allegations, fail to state a claim.

D. Causation

The court is cognizant of the fact that the '864 Patent is not the only Orange Book listing and litigated patent the plaintiffs complain of. In fact, the Second Amended Complaint adds even more Orange Book listing claims, asserting that "[e]ven after Sanofi's litigation with Lilly, it expected other companies would soon seek to create affordable follow-on insulin glargine products. To further frustrate those efforts, Sanofi obtained and then listed in the Orange Book an additional *thirteen* patents over its SoloSTAR injector pen." SAC ¶ 389 (emphasis in original). These Sherman Act claims, as based on these other patents, fail for lack of causation.

"An antitrust plaintiff must prove a causal connection between the antitrust violation and actual damages suffered." In re Wellbutrin XL Antitrust Litig., Nos. 08-2431, 08-2433, 2012 WL 1657734, at *33 (E.D.P.A. May 11, 2012). In an antitrust class action, "individual injury (also known as antitrust impact) is an element of the cause of action; to prevail on the merits, every class member must prove at least some antitrust impact resulting from the alleged violation." In re Hydrogen Peroxide Antitrust Litig., 552 F.3d 305, 311 (3d Cir. 2008). The plaintiffs have alleged harm from Sanofi's practices "between February 13, 2015 and December 31, 2016 or until the anticompetitive effects of Sanofi's conduct cease[.]" SAC ¶ 486. As addressed above, the plaintiffs have failed to state a plausible claim for relief based on the listing of the '864 Patent or the litigation enforcing that patent against Lilly, which ended in a settlement agreement that delayed Lilly's market entry until December 2016.

The plaintiffs argue that even if Sanofi's conduct related to the '864 Patent were valid, the thirty-month stay provided for by statute expired on June 20, 2016, six months prior to Lilly's product coming to market. Opp. at 34-35. The plaintiffs seem to be arguing that there were damages during that additional period for which the '864 Patent was not an independent bar. That delay, however, was the product of a settlement agreement entered into between the parties in Sanofi I on September 28, 2015, well before the expiration of the stay. SAC ¶ 375. As explained above, when a party sues on a paragraph IV certification, as Sanofi did here, "the FDA will not grant final approval to the [new drug application] until the earlier of (a) the passage of 30 months, or (b) the issuance of a decision by a court that the patent is invalid or not infringed by the [new] product." 21 U.S.C. § 355(c)(3)(C). Where, as here, the court endorsed a settlement prior to the expiration of 30 months, Sanofi is entitled to any additional delay embodied in that settlement.

Thus, the '864 Patent, and the settlement based thereon, stood as a lawful bar to Lilly's market entry, and the plaintiffs cannot show that Sanofi's conduct related to any other patent caused harm from Lilly's delay during that time period. Additionally, in light of this court's dismissal of the plaintiffs' serial petitioning claim alleging harm from the Merck and Mylan suits, the plaintiffs have failed to show that Sanofi can be held liable for actions causing market delay after December 31, 2016.

E. Claim of Overall Scheme

Finally, the court addresses the fact that the plaintiffs have not simply alleged that the Orange Book listings and the litigations against Lilly, Merck, and Mylan violated the antitrust laws, but that these actions collectively create an "illegal scheme to prevent, delay, and/or

minimize the success of the introduction into the United States marketplace of any competing versions of [] insulin glargine products[.]" SAC ¶ 502. A court "can consider the individual aspects of [a scheme] claim so long as it keeps the larger scope of the scheme in context." In re Asacol Antitrust Litig., 233 F. Supp. 3d 247, 261 (D. Mass. 2017). "In antitrust cases in which a scheme is alleged, 'plaintiffs should be given the full benefit of their proof without tightly compartmentalizing the various factual components and wiping the slate clean after scrutiny of each.'" Id. (quoting Cont'l Ore Co. v. Union Carbide & Carbon Corp., 370 U.S. 690, 698-99, 82 S. Ct. 1404, 1410, 8 L. Ed. 2d 777 (1962)). However, "if all we are shown is a number of perfectly legal acts, it becomes much more difficult to find overall wrongdoing. Similarly, a finding of some slight wrongdoing in certain areas need not by itself add up to a violation. We are not dealing with a mathematical equation. We are dealing with what has been called the 'synergistic effect' of the mixture of the elements." City of Anaheim v. S. Cal. Edison Co., 955 F.2d 1373, 1376 (9th Cir. 1992) (quoting City of Groton v. Conn. Light & Power Co., 662 F.2d 921, 929 (2d Cir. 1981).

A consideration of the overall mixture of alleged conduct in this case does not warrant a different conclusion than does the evaluation of each element. As shown above, the plaintiffs have not plausibly shown that Sanofi engaged in the improper practice of Orange Book listing and suing competitors to cause anticompetitive injury. The plaintiffs' antitrust claims, as premised on an overall scheme of improper listings and improper litigations, are dismissed.

F. Market Power

As the court concludes that the Second Amended Complaint fails to adequately plead an improper means of acquiring monopoly power, this court need not address the parties'

arguments over whether the plaintiffs have adequately pled that Sanofi possessed monopoly power in the relevant market.

V. CONCLUSION

For the reasons herein, the plaintiffs have failed to state a claim on which relief can be granted for monopolization or attempted monopolization. The Motion to Dismiss (Docket No. 54) is hereby ALLOWED and the Second Amended Complaint is dismissed with prejudice.

/ s / Judith Gail Dein
Judith Gail Dein
United States Magistrate Judge

US005656722A

United States Patent [19]

Dörschug

[11] Patent Number: 5,656,722

[45] Date of Patent: Aug. 12, 1997

[54] A^{21}-, B^{30} - MODIFIED INSULIN DERIVATIVES HAVING AN ALTERED ACTION PROFILE

[75] Inventor: **Michael Dörschug**, Bochum, Germany

[73] Assignee: **Hoechst Aktiengesellschaft**, Frankfurt am Main, Germany

[21] Appl. No.: **304,593**

[22] Filed: **Sep. 12, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 46,481, Apr. 9, 1993, abandoned, which is a continuation of Ser. No. 929,510, Aug. 19, 1992, abandoned, which is a continuation of Ser. No. 431,844, Nov. 6, 1989, abandoned.

[30] **Foreign Application Priority Data**

Nov. 8, 1988 [DE] Germany 38 37 825.6

[51] **Int. Cl.**[6] **A61K 38/28**

[52] **U.S. Cl.** **530/303**; 530/304

[58] **Field of Search** 530/303, 304; 514/3, 12

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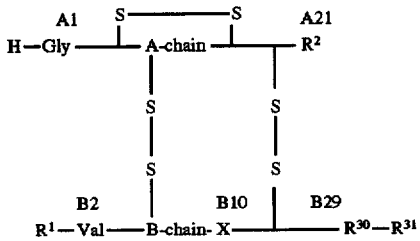
Primary Examiner—David Lukton

Attorney, Agent, or Firm—Finnegan, Henderson, Farabow, Garrett & Dunner, L.L.P.

[57] ABSTRACT

New insulin derivatives, the use thereof, and a pharmaceutical composition containing them

Insulin derivatives having an isoelectric point between 5 and 8.5, or physiologically tolerated salts thereof, of the Formula II



in which:

R^1 at position B1 denotes H or H-Phe;

R^2 at position A21 denotes a genetically encodable L-amino acid selected from the group consisting of Gly, Ala, Val, Leu, Ile, Pro, Phe, Trp, Met, Ser, Thr, Cys, Tyr, Asp, and Glu;

R^{30} represents the residue of a neutral genetically encodable L-amino acid selected from the group consisting of Ala, Thr, and Ser;

R^{31} represents 1, 2, or 3 neutral or basic alpha amino acids, wherein at least one of the alpha amino acids is selected from the group consisting of Arg, Lys, Hyl, Orn, Cit, and His;

X represents His at position B10; and

the sequences A1 to A20 and B1 to B29 in Formula II correspond to a mammalian insulin;

excluding those insulin derivatives in which simultaneously:

R^1 at position B1 denotes Phe; and

R^3 is one alpha amino acid having a terminal carboxyl group.

15 Claims, No Drawings

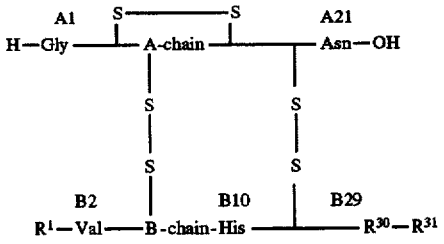
A^{21}-, B^{30} - MODIFIED INSULIN DERIVATIVES HAVING AN ALTERED ACTION PROFILE

This application is a continuation, of application Ser. No. 08/046,481 filed Apr. 9, 1993, abandoned, which is a continuation of application Ser. No. 07/929,510, filed Aug. 19, 1992, abandoned, which is a continuation of application Ser. No. 07/431,844, filed Nov. 6, 1989, now abandoned.

BACKGROUND OF THE INVENTION

As is known, insulin and insulin derivatives are required in considerable quantities for the treatment of the disease diabetes mellitus, and some of them are also produced on an industrial scale. Despite the considerable number of insulin compositions and modifications with different action profiles which are already in existence, there is still a need, because of the variety of organisms with their inter- and intraindividual variations, for other insulin products which in turn have other properties and action characteristics.

Insulin derivatives with a delayed action are described, for example, in EP-B 132,769 and EP-B 132,770. These are specifically derivatives with a basic modification in position B31 of the insulin B chain, of the following formula I:



in which R^1 denotes H or H-Phe, R^{30} represents the residue of a neutral, genetically encodable L-amino acid, and R^{31} represents a physiologically acceptable organic group which is basic in nature and has up to 50 carbon atoms, in whose structure 0 to 3 α-amino acids are involved and whose terminal carboxyl group which is present where appropriate can be free, in the form of an ester functionality, an amide functionality, a lactone or reduced to CH_2OH.

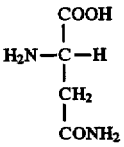
Characteristic of these insulin derivatives is an isoelectric point between 5.8 and 8.5 (measured by isoelectric focusing). The fact that the isoelectric point is shifted from the isoelectric point of unmodified natural insulin or proinsulin (at pH=5.4) into the neutral range derives from the additional positive charge(s) located on the surface of the molecule as a result of the basic modification. This makes these insulin derivatives with a basic modification less soluble in the neutral range than, say, natural insulin or proinsulin, which are normally dissolved in the neutral range.

The delaying or depot action of the insulin derivatives with a basic modification, of the formula I, derives from their sparing solubility at the isoelectric point. According to the two abovementioned publications, the redissolution of the insulin derivatives under physiological conditions is achieved by elimination of the additional basic groups, which is brought about, depending on the derivative, by trypsin or trypsin-like and/or carboxypeptidase B or carboxypeptidase B-like and/or esterase activity. The eliminated groups are in each case either purely physiological metabolites or else easily metabolized physiologically acceptable substances.

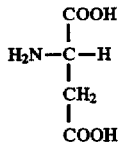
The abovementioned depot principle resulting from basic modification of the insulin has also been further utilized by the provision and corresponding use of other insulin derivatives with basic modifications, mainly within the A and B chains; cf. for example EP-A 0,194,864 and EP-A 0,254,516.

In the insulin derivatives specified in EP-A 0,194,864, a basic amino acid is incorporated in the B27 position and/or a neutral amino acid is located at positions A4, A17, B13 and/or B21; in addition, the C-terminal carboxyl group of the B chain is blocked by an amide or ester residue.

The insulin derivatives specified in EP-A 0,254,516 are very similar to those specified in the abovementioned EP-A; however, in this case, with the aim of increasing the stability of the relevant pharmaceutical compositions at the weakly acid pH values, the amino acid Ash in position A21 can also be replaced by other amino acids which are more stable in acid medium, such as, for example, Asp. As is known, Ash (=asparagine) differs from Asp (=aspartic acid) by the blocking of one of the two carboxyl groups by the amide group:



asparagine



aspartic acid

Rapid-acting insulin derivatives are said to result from yet another modification of the insulin molecule in the A and B chain, in particular by replacing the amino acid His, which is responsible for the formation of a complex with zinc—and thus for a certain delaying action, in the B10 position by other appropriate amino acids; cf. EP-A 0,214,826.

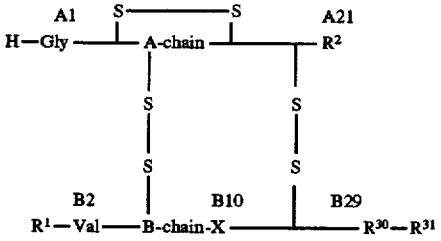
All the insulin derivatives specified in the 3 lastmentioned publications are mainly modified within the A and B chains; they are prepared by genetic engineering routes.

SUMMARY OF THE INVENTION

In the attempt to increase the stability in acid medium of the insulin derivatives with a basic modification on the C-terminal end of the B chain as specified in the European Patents EP-B 0,132,769 and EP-B 0,132,770 mentioned in the introduction, and, where appropriate, also to alter the action profile thereof, it has now been found that this object is achieved in an advantageous manner by replacing Asn^{A21} by other genetically encodable amino acids which contain no amide group and, where appropriate, by replacing His^{B10} by other genetically encodable amino acids.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Hence the invention relates to insulin derivatives of the formula II



in which:

R^1 denotes H or H-Phe,

R^2 denotes a genetically encodable L-amino acid which contains no amide group,

R^{30} represents the residue of a neutral genetically encodable L-amino acid,

R^{31} represents a physiologically acceptable organic group which is basic in nature and has up to 50 carbon atoms, in whose structure 0 to 3 α-amino acids are involved and whose terminal carboxyl group which is present where appropriate can be free, in the form of an ester functionality, an amide functionality, a lactone or reduced to CH_2OH, and

X represents a genetically encodable L-amino acid, having an isoelectric point between 5 and 8.5, and the physiologically tolerated salts thereof.

The new insulin derivatives and the physiologically tolerated salts thereof are stable at the weakly acid pH values of appropriate pharmaceutical compositions even for extended periods and have—especially when His^{B10} has also been replaced by other amino acids—an altered (shorter) action profile compared with the known—unaltered—insulin derivatives with a basic modification of the formula I indicated in the introduction.

R^1 in formula II is preferably H-Phe.

Genetically encodable L-amino acids containing no amide group—for R^2 —are Gly, Ala, Ser, Thr, Val, Leu, Ile, Asp, Glu, Cys, Met, Arg, Lys, His, Tyr, Phe, Trp, Pro;

Gly, Ala, Ser, Thr, Asp and Glu are preferred, especially Asp.

Neutral genetically encodable L-amino acids—for R^{30}— are Gly, Ala, Ser, Thr, Val, Leu, Ile, Ash, Gln, Cys, Met, Tyr, Phe and Pro; Ala, Thr and Set are preferred.

R^{31} is a physiologically acceptable organic group which is basic in nature and has up to 50 carbon atoms and in whose structure 0–3 α-amino acids are involved. When no α-amino acids are involved in the structure of R^{31}, examples of suitable basic groups for this residue are the following:

amino-(C_2–C_6)-alkoxy, (C_1–C_4)-alkylamino-(C_2–C_6)-alkoxy, di-(C_1–C_4)-alkylamino-(C_2–C_6)-alkoxy, tri-(C_1–C_4) ammonio-(C_2–C_6)-alkoxy, amino-(C_2–C_6)-alkylamino, [(C_1–C_4)-alkyl-amino]- (C_2–C_6)-alkylamino, di-(C_1–C_4)-alkylamino-(C_2–C_6)-alkylamino or [tri-(C_1–C_4)-alkylamino]-(C_2–C_6)-alkylamino, especially —O—[CH_2]—NR_2 and —O—[CH_2]—$N^{30}R_3$, —NH—[CH_2]$_p$—NR_2 or —NH—[CH_2]$_p$—$^+R_3$, in which p is 2 to 6, and R is identical or different and represents hydrogen or (C_1–C_4)-alkyl.

When up to 3 α-amino acids are involved in the structure of R^{31} , these are primarily neutral or basic naturally occurring L-amino acids and/or the D-amino acids corresponding thereto. Neutral naturally occurring amino acids are, in particular, Gly, Ala, Ser, Thr, Val, Leu, Ile, Ash, Gln, Cys, Met, Tyr, Phe, Pro and Hyp. Basic naturally occurring amino acids are, in particular, Arg, Lys, Hyl, Orn, Cit and His. If only neutral α-amino acids are involved, the terminal carboxyl group thereof cannot be free—in order for R^{31} to be basic in nature; on the contrary, the carboxyl group must in this case be amidated or esterified with a basic group,

suitable basic groups for this being, for example, the abovementioned basic groups—in the case where no α-amino acids are involved in the structure of R^{31}. Of course, these basic ester or amide groups can also block the carboxyl group of basic α-amino acids. Also possible and suitable for blocking the carboxyl group of the basic α-amino acids are—if the blocking is desired—neutral ester or amide groups such as, for example, (C_1–C_6)-alkoxy, (C_3–C_6)-cycloalkyloxy, NH_2, (C_1–C_6)-alkylamino or di-(C_1–C_6)-alkylamino.

Of course, the terminal carboxyl group can be in the form of a lactone only if the terminal amino acid is a hydroxyamino acid.

Moreover, the terminal carboxyl group can also be reduced to CH_2OH.

R^{31} is preferably composed of 1, 2 or 3 of the abovementioned basic naturally occurring amino acids; R^{31} is particularly preferably Arg-OH or Arg-Arg-OH.

Suitable genetically encodable L-amino acids—for X—are the same amino acids as for R^2, but the genetically encodable L-amino acids which contain an amide group—which are Ash and Gln—are also possible in this case; the latter—Asn and Gln—are in fact preferred in this case. If Asn or Gln is located in position B10, the amide group is at least stable in weakly acid medium (in contrast to Asn or Gln in position A21). The sequences (A1–A20) and (B1–B9, B11–B29) are preferably the sequences of human, porcine or bovine insulin, especially the sequences of human insulin.

Examples of insulin derivatives of the formula II are:

Asp^{A21}-Human insulin-Arg^{B31}—OH
Glu^{A21}-Human insulin-Arg^{B31}—OH
Gly^{A21}-Human insulin-Arg^{B31}—OH
Ser^{A21}-Human insulin-Arg^{B31}—OH
Thr^{A21}-Human insulin-Arg^{B31}—OH
Ala^{A21}-Human insulin-Arg^{B31}—OH
Asp^{A21}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Glu^{A21}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Gly^{A21}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Ser^{A21}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Thr^{A21}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Ala^{A21}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Asp^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—OH
Glu^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—OH
Gly^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—OH
Ser^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—OH
Thr^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—OH
Ala^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—OH
Asp^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Glu^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Gly^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Ser^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Thr^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—Arg^{B32}—OH
Ala^{A21}—Asn^{B10}-Human insulin-Arg^{B31}—Arg^{B32}—OH

The insulin derivatives of the formula II are prepared mainly by a genetic manipulation by means of site-directed mutagenesis using standard methods.

For this purpose, a gene structure coding for the desired insulin derivative of the formula II is constructed and its expression is brought about in a host cell—preferably in a bacterium such as *E. coli* or a yeast, in particular *Saccharomyces cerevisiae*—and—if the gene structure codes for a fusion protein—the insulinderivative of the formula II is liberated from the fusion protein; analogous methods are described, for example, in EP-A 0,211,299, EP-A 0,227,938, EP-A 0,229,998, EP-A 0,286,956 and German Patent Application P 38 21 159.9 dated Jun. 23, 1988 (HOE 88/F 158).

After cell disruption, the fusion protein portion is eliminated either chemically using cyanogen halide—cf. EP-A 0,180,920 or enzymatically using lysostaphin—cf. DE-A 3,739,347.

The insulin precursor is then subjected to oxidative sulfitolysis by the method described, for example, by R. C. Marshall and A. S. Inglis in "Practical Protein Chemistry—A Handbook" (edited by A. Darbre) 1986, pages 49–53, and subsequently renatured in the presence of a thiol with the formation of the correct disulfide bridges, for example by the method described by G. H. Dixon and A. C. Wardlow in Nature (1960), pages 721–724.

The C peptide is removed by cleavage with trypsin—for example by the method of Kemmler et al., J. B. C. (1971), pages 6786–6791, and the insulin derivative of the formula II is purified by known techniques such as chromatography—cf., for example, EP-A-0,305,760—and crystallization.

The insulin derivatives of the formula II with R^2=Asp and X=His are expediently prepared by hydrolysis of the known insulin derivatives which have a basic modification and the formula I in aqueous acidic medium (because only the amide group of the asparagine in position A21 must be hydrolyzed in this case), preferably at pH values between about 2 and about 4, in particular of about 2.5, and at temperatures of about 0° to about 40° C., preferably at room temperature.

The insulin derivatives of the formula II, according to the invention, and/or the physiologically tolerated salts thereof (such as, for example, the alkali metal or ammonium salts) are mainly used as active substances for a pharmaceutical composition for the treatment of diabetes mellitus.

The pharmaceutical composition is preferably a solution or suspension for injection; it contains at least one insulin derivative of the formula II and/or at least one of the physiologically tolerated salts thereof in dissolved, amorphous and/or crystalline—preferably in dissolved—form.

The composition preferably has a pH between about 2.5 and 8.5, in particular between about 4.0 and 8.5, and contains a suitable tonicity agent, a suitable preservative and, where appropriate, a suitable buffer, as well preferably a certain zinc ion concentration, all, of course, in sterile aqueous solution. All the ingredients of the composition apart from the active substance form the composition vehicle.

Examples of suitable tonicity agents are glycerol, glucose, mannitol, NACl, and calcium or magnesium compounds such as $CaCl_2$, $MgCl_2$ etc.

The choice of the tonicity agent and/or preservative influences the solubility of the insulin derivative or the physiologically tolerated salt thereof at the weakly acid pH values.

Examples of suitable preservatives are phenol, m-cresol, benzyl alcohol and/or p-hydroxybenzoic esters.

Examples of buffer substances which can be used, in particular for adjusting a pH between about 4.0 and 8.5, are sodium acetate, sodium citrate, sodium phosphate etc. Otherwise, also suitable for adjusting the pH are physiologically acceptable dilute acids (typically HCl) or alkalis (typically NaOH).

When the composition contains zinc a content of 1 µg to 2 mg, in particular from 5 µg to 200 µg, of zinc/ml is preferred.

In order to vary the action profile of the composition according to the invention it is also possible to admix unmodified insulin, preferably bovine, porcine or human insulin, in particular human insulin.

Preferred concentrations of active substance are those corresponding to about 1–1500, also preferably about 5–1000, and in particular about 40–400, international units/ml.

The invention is now explained in detail by the examples which follow.

A) Preparation By Genetic Manipulation

EXAMPLE 1

Construction of a plasmid for the preparation of Gly (A21)-human insulin Arg (B31-OH)

The plasmid pSW3 has been described in German Patent Application P 38 21 159.9 (HOE 88/F 158). The plasmid DNA is reacted with the restriction enzymes PvuII and SalI and subsequently treated with bovine alkaline phosphatase. The two resulting fragments are separated by gel electrophoresis, and the large fragment is isolated. This fragment is linked in a T4 DNA ligase reaction with the following synthetic DNA sequence:

```
5'- CTG GAA AAC TAC TGT GGT TGA TAG
    GAC CTT TTG ATG ACA CCA ACT ATC AGCT - 5'
```

Competent *E. coli* W3110 cells are transformed with the ligation mixture. The transformation mixture is plated out on NA plates which contain 20 µg of Ap (=Ampicillin)/ml and incubated at 37° C. overnight. An overnight culture is obtained from single colonies, and plasmid DNA is obtained from this. This DNA is characterized by means of restriction analysis and DNA sequence analysis. Correct plasmids which encode the modified A chain are called pIK100. Expression is carried out in analogy to Example 3 of the abovementioned German Patent Application P 38 21 159.9. The modified mono-Arg-insulin is likewise prepared in analogy to the preparation of the unmodified mono-Arg-insulin described in this German Patent Application.

EXAMPLE 2

Construction of a plasmid for the preparation of Ser (A21)- human insulin (Arg B31-OH)

The construction corresponds to the route described in the above example. The synthetic DNA sequence is, however, modified as follows:

```
5' - CTG GAA AAC TAC TGT TCA TGA TAG
     GAC CTT TTG ATG ACA AGT ACT ATC AGCT - 5'
```

The plasmid pIK110 which has an additional BspHI recognition sequence is obtained.

EXAMPLE 3

Construction of a plasmid for the preparation of Gly (A21)- Asn(B10)-human insulin Arg(B31-OH)

DNA from the plasmid pIK100 is cleaved with the restriction enzymes HpaI and DraIII and treated with bovine alkaline phosphatase. The two resulting fragments are separated by gel electrophoresis, and the larger of the two fragments is isolated. The fragment is ligated with the synthetic DNA sequence

```
5' - AAC CAA CAC TTG TGT GGT TCT AAC TTG
     TTG GTT GTG AAC ACA CCA AGA TTG      - 5'
```

and competent *E. coli* W3110 cells are transformed with the ligation mixture. Further characterization of the resulting plasmid pIK101 is carried out as described in Example 1.

EXAMPLE 4

Construction of a plasmid for the preparation of Ser (A21)- Asn(B10)-human insulin

The construction corresponds to the cloning described in Example 3, but starting from DNA from the plasmid pIK110. The newly constructed plasmid is called pIK111.

EXAMPLE 5

Construction of an expression plasmid for monkey proinsulin

Monkey proinsulin differs from human proinsulin merely by replacement of a single amino acid in the C peptide (B37-Pro in place of Leu in this position of human proinsulin).

The plasmid pSW3 is opened with HpaI and SalI and the remaining plasmid DNA is isolated. The DraIII-SalI monkey proinsulin fragment is isolated from the plasmid pK50 described in EP-A0.229,998. The two fragments are linked to the synthetic DNA fragment

5' - AAC CAG CAC CTG TGC GGT TCT CAC CTA
TTG GTC GTG GAC ACG CCA AGA GTG - 5'

in a T4 DNA ligase reaction. The plasmid pSW2 is obtained, and its DNA is used hereinafter as starting material for the constructions of the expression plasmids encoding the di-Arg-human insulin derivatives.

EXAMPLE 6

Construction of a plasmid for the preparation of Gly(A21) -human insulin Arg(B31)-Arg(B32)-OH

DNA of the plasmid pSW2 is cleaved with PvuII and SalI in accordance with Example 1 and ligated with the synthetic DNA from Example 1; the result is the plasmid pSW21.

EXAMPLE 7

Construction of a plasmid for the preparation of Ser(A21) -human insulin-Arg(B31)-Arg(B32)-OH

The plasmid pSW22 is constructed starting from pSW2 DNA in analogy to Example 2.

EXAMPLE 8

Construction of a plasmid for the preparation of Gly(A21) -Asn(B10)-human insulin-Arg(B31)-Arg(B32)-OH

The plasmid pSW23 is constructed starting from pSW21 DNA in analogy to Example 3.

The following sequence is used as synthetic DNA sequence for this:

5' - AAC CAA CAC TTG TGT GGT TCT AAC CTA
TTG GTT GTG AAC ACA CAA AGA TTG -5'

EXAMPLE 9

Construction of a plasmid for the preparation of Set(A21) -Asn(B10)-human insulin-B31(Arg)-B32(Arg)-OH

The plasmid pSW24 is constructed starting from pSW22 DNA in analogy to Example 4 using the synthetic DNA sequence described in Example 8.

B) Preparation of Asp^{A21}-Human Insulin-Arg^{B31}-Arg^{B32}-OH From Human Insulin-Arg^{B31} -Arg^{B32} -OH by Hydrolysis

1 g of human insulin-Arg^{31}-Arg^{32}-OH is suspended in 100 ml of H_2O. The pH is adjusted to 2.5 by addition of HCl, and the solution is left at 37° C. After one week about one half of the material has been converted into Asp^{A21}-human insulin-$Arg^{B31}Arg^{B32}$-OH. The product is separated from the starting material in a manner known per se on an anion exchanger, is precipitated from the eluate and is crystallized in a buffer which contains 10.5 g of citric acid, 1 g of phenol

and 5 ml of a 1% strength zinc chloride solution per liter with a protein concentration of 5 g/l at pH 6.0. The yield is 390 mg of Asp^{A21}-human insulin-Arg^{B31}-Arg^{B32}.

C) Preparation of an Injection Solution

The insulin derivative from B is dissolved at a concentration of 1.4 mg/ml in a sterile vehicle solution of the following composition (per ml):

18 mg of glycerol, 10 mg of benzyl alcohol, 80 µg of Zn^{2+}, pH 4.0.

D) Action Profile of an Asp^{A21}-Human Insulin-Arg^{B31}-Arg^{B32}-OH Composition in dogs by comparison with human insulin-Arg^{B31}-Arg^{B32}-OH and basal H insulin Hoechst$^{(R)}$= an NPH (neutral protamine Hagedorn) composition containing about 10 µg of Zn^{2+}.

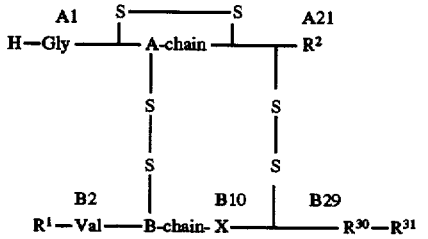
		Blood glucose as a % of the initial level in hours (h)				
Product		1 h	2 h	3 h	5 h	7 h
According to the invention	Asp^{A21}-human insulin Arg^{B31}—Arg^{B32}—OH	99	62	51	75	98
Comparison	Human insulin Arg^{B31}—Arg^{B32}—OH	77	52	64	85	98
	Basal H insulin Hoechst$^{(R)}$	71	49	59	83	100

This example shows that Asp^{A21}-human insulin-Arg^{B31}-Arg^{B32}-OH has the same advantageous basal profile as human insulin-Arg^{B31}-Arg^{B32}-OH. In addition, Asp^{A21}-human-insulin-Arg^{B31}-Arg^{B32}-OH has the advantageous property that the compound is stable for a long time under the chosen conditions.

I claim:

1. An insulin derivative having an isoelectric point between 5 and 8.5, or a physiologically tolerated salt thereof, of the Formula II

in which:



R^1 at position B1 denotes H or H-Phe;

R^2 at position A21 denotes a genetically encodable L-amino acid selected from the group consisting of Gly, Ala, Val,

Leu, Ile, Pro, Phe, Trp, Met, Ser, Thr, Cys, Tyr, Asp, and Glu;

R^{30} represents the residue of a neutral genetically encodable L-amino acid selected from the group consisting of Ala, Thr, and Ser;

R^{31} represents 1, 2, or 3 neutral or basic α-amino acids, wherein at least one of the α-amino acids is selected from the group consisting of Arg, Lys, Hyl, Orn, Cit, and His;

X represents His at position B10; and the sequences A1 to A20 and B1 to B29 in Formula II correspond to a mammalian insulin;

excluding those insulin derivatives in which simultaneously:

R^1 at position B1 denotes Phe; and

R^{31} is one alpha amino acid having a terminal carboxyl group.

2. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein R^1 in formula II represents H-Phe.

3. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein R^2 in formula II represents Gly, Ala, Ser, Thr, Asp, or Glu.

4. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein R^{31} in formula II represents Arg-Arg-OH.

5. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **1**, wherein the sequences (A1 to A20) and (B1 to B29) in formula II are the sequences of human, porcine, or bovine insulin.

6. A pharmaceutical composition that contains an effective amount of at least one insulin derivative of the formula II, or at least one of the physiologically tolerated salts thereof, as claimed in claim **1**, in dissolved, amorphous or crystalline form for the treatment of diabetes.

7. A pharmaceutical composition as claimed in claim **6**, which additionally contains 1 μg to 2 mg of zinc/ml.

8. A pharmaceutical composition as claimed in claim **6**, which additionally contains unmodified insulin.

9. A method for treating a patient suffering from diabetes mellitus, which comprises administering to said patient a pharmaceutical composition as claimed in claim **6**.

10. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **3**, wherein R^2 in formula II represents Asp.

11. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **5**, wherein the sequences (A1 to A20) and (B1 to B29) in formula II are the sequences of human insulin.

12. A pharmaceutical composition that contains an effective amount of at least one insulin derivative of the formula II, or at least one of the physiologically tolerated salts thereof, as claimed in claim **8**, in dissolved form for the treatment of diabetes.

13. A pharmaceutical composition as claimed in claim **7**, which additionally contains 5 μg to 200 μg of zinc/ml.

14. A pharmaceutical composition as claimed in claim **8**, wherein said unmodified insulin is unmodified human insulin.

15. An insulin derivative or the physiologically tolerated salts thereof as claimed in claim **5**, wherein R^1 represents H-Phe, R^2 represents Gly, R^{30} represents Thr, and R^{31} represents Arg-Arg-OH.

* * * * *

US008556864B2

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

(10) **Patent No.: US 8,556,864 B2**
(45) **Date of Patent: *Oct. 15, 2013**

(54) **DRIVE MECHANISMS SUITABLE FOR USE IN DRUG DELIVERY DEVICES**

(75) Inventors: **Robert Frederick Veasey**, Warwickshire (GB); **Robert Perkins**, Warwickshire (GB); **David Aubrey Plumptre**, Worcestershire (GB)

(73) Assignee: **Sanofi-Aventis Deutschland GmbH**, Frankfurt am Main (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 301 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/075,212**

(22) Filed: **Mar. 30, 2011**

(65) **Prior Publication Data**

US 2011/0178474 A1 Jul. 21, 2011

Related U.S. Application Data

(63) Continuation of application No. 11/520,598, filed on Sep. 14, 2006, now Pat. No. 7,935,088, which is a continuation of application No. 10/790,866, filed on Mar. 3, 2004, now abandoned.

(30) **Foreign Application Priority Data**

Mar. 3, 2003 (GB) 0301822.0

(51) **Int. Cl.**
A61M 5/00 (2006.01)

(52) **U.S. Cl.**
USPC **604/207**; 604/208

(58) **Field of Classification Search**
USPC 604/207–211, 224, 246
See application file for complete search history.

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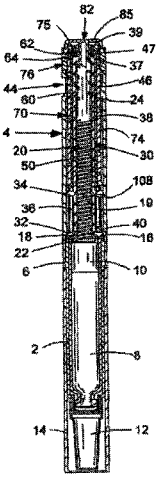
Primary Examiner — Kevin C Sirmons
Assistant Examiner — Andrew Gilbert
(74) *Attorney, Agent, or Firm* — McDonnell Boehnen Hulbert & Berghoff LLP

(57) **ABSTRACT**

A drive mechanism suitable for use in drug delivery devices is disclosed. The drive mechanism may be used with injector-type drug delivery devices, such as those permitting a user to set the delivery dose. The drive mechanism may include a housing, a dose dial sleeve, and a drive sleeve. A clutch is configured to permit rotation of the drive sleeve and the dose dial sleeve with respect to the housing when the dose dial sleeve and drive sleeve are coupled through the clutch. Conversely, when the dose dial sleeve and drive sleeve are in a de-coupled state, rotation of the dose dial sleeve with respect to the housing is permitted and rotation of the drive sleeve with respect to the housing is prevented. In the de-coupled state, axial movement of the drive sleeve transfers force in a longitudinal direction for actuation of a drug delivery device.

10 Claims, 13 Drawing Sheets



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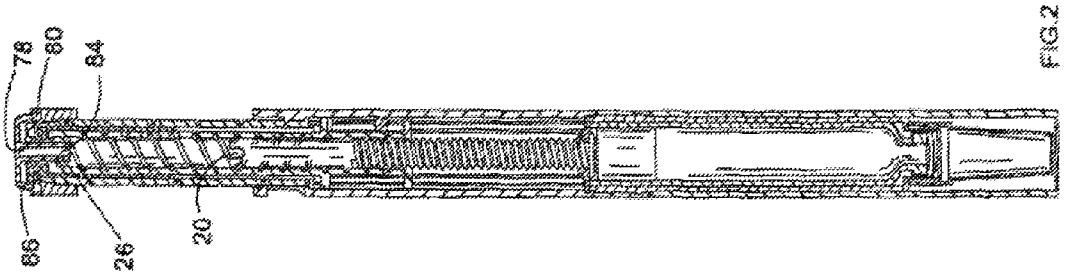
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FIG.2

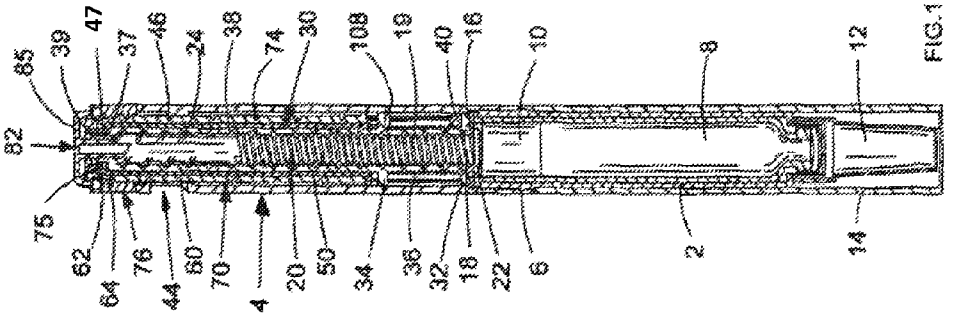
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FIG.1

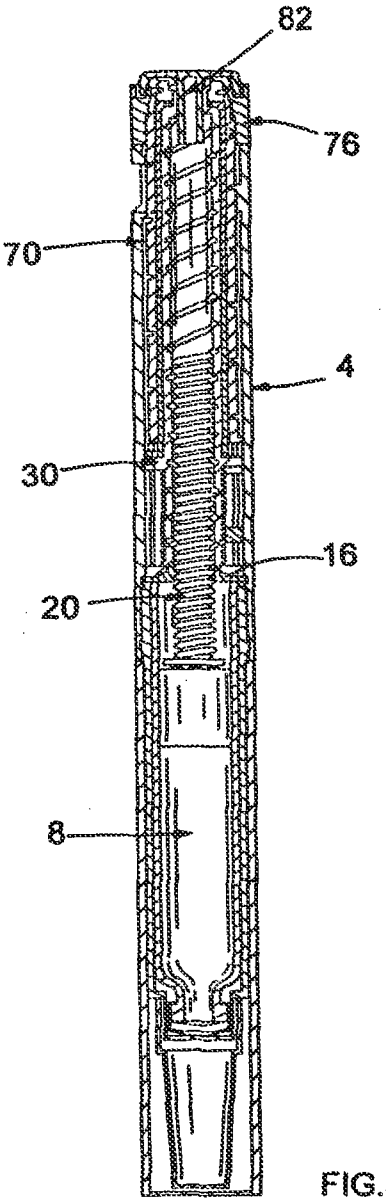

FIG.3

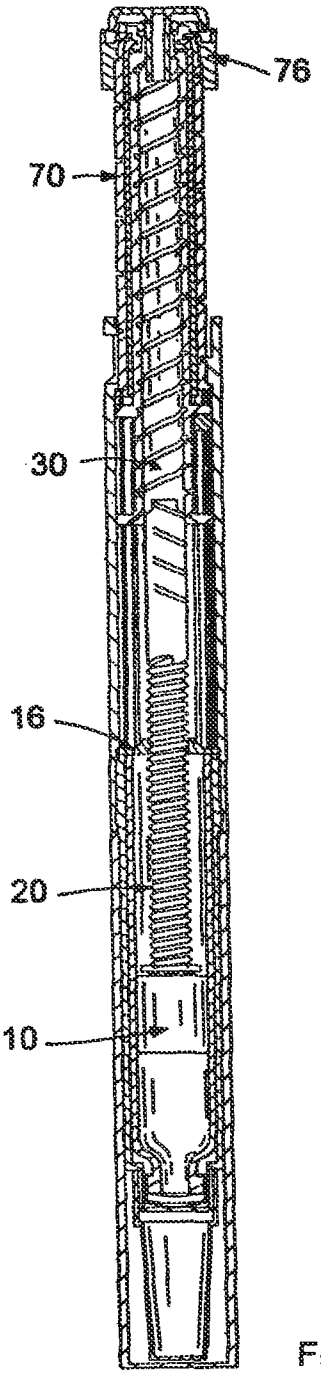

FIG.4

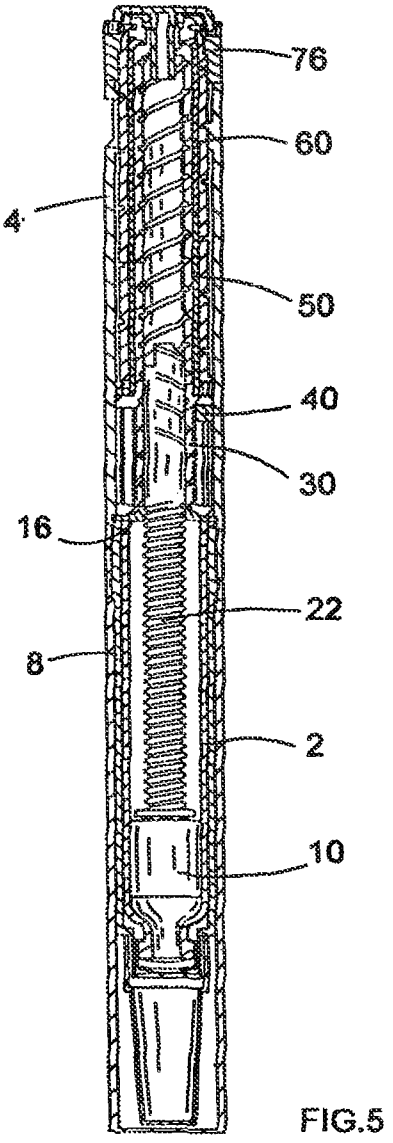

FIG.5

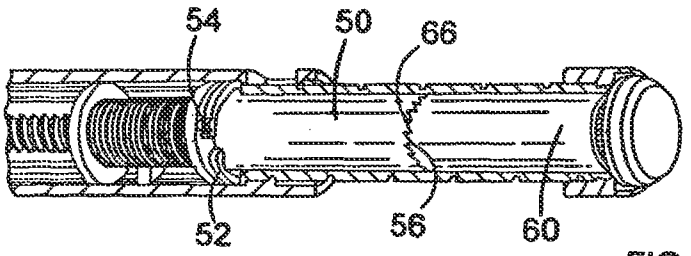

FIG.6

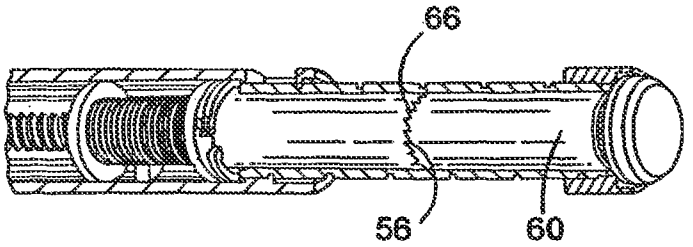

FIG.7

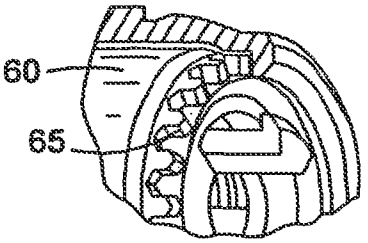

FIG.8

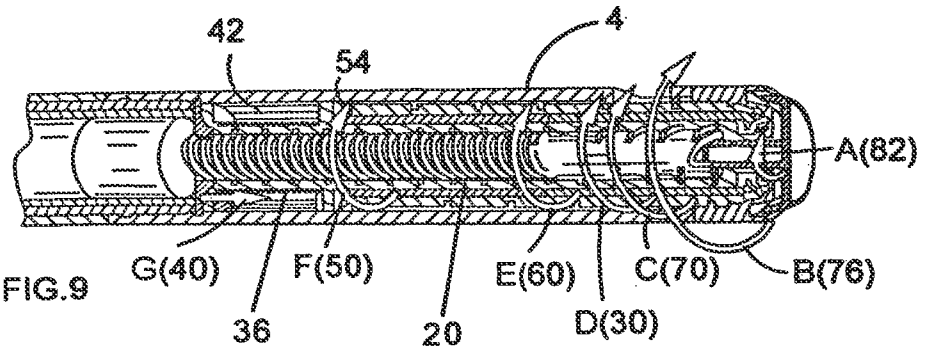

FIG.9

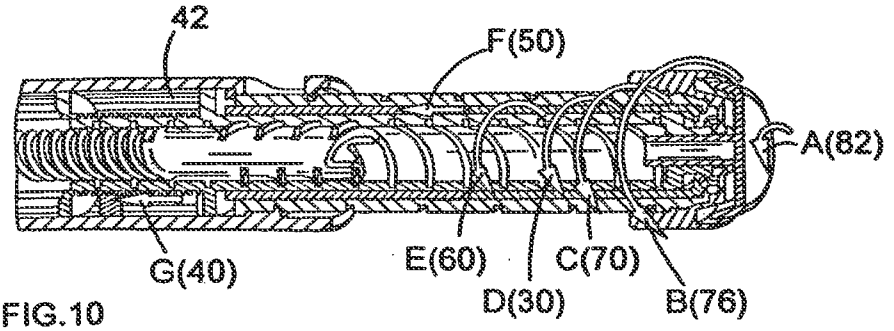

FIG.10

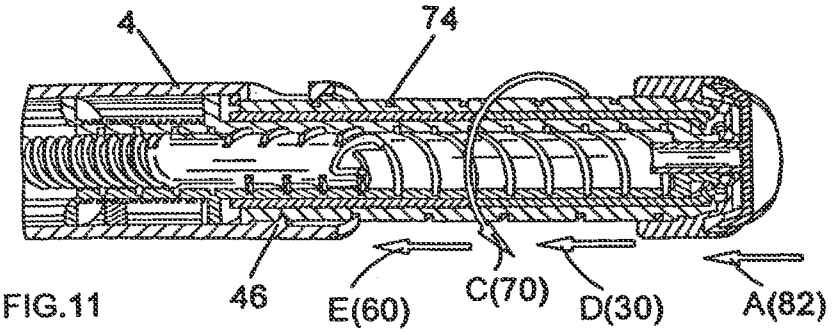

FIG.11

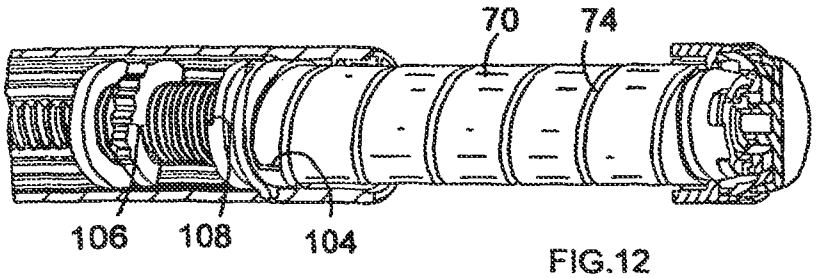

FIG.12

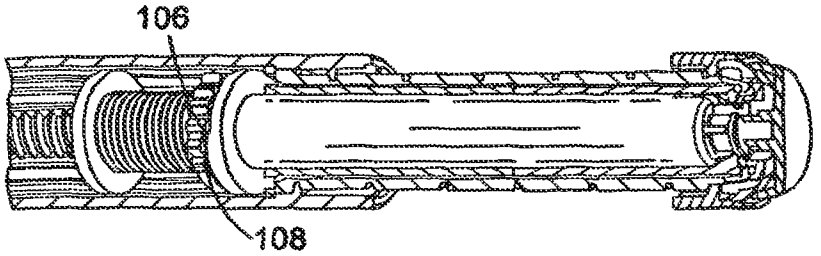

FIG.13

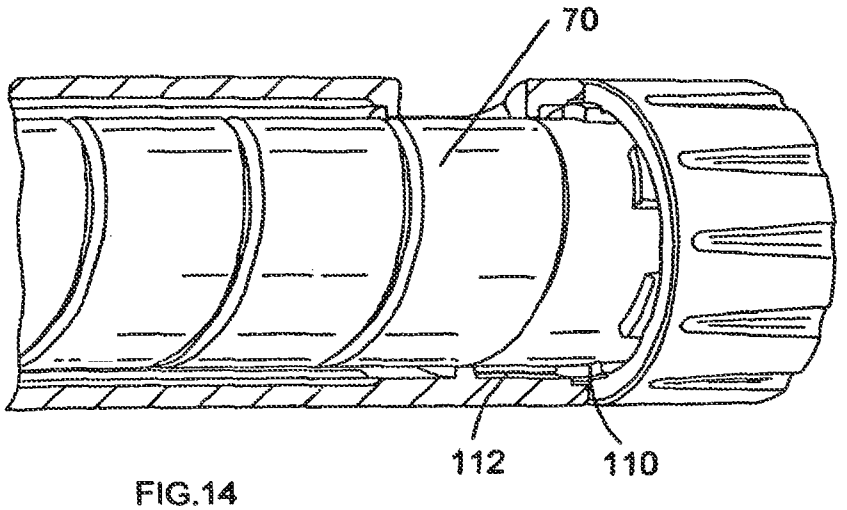

FIG.14

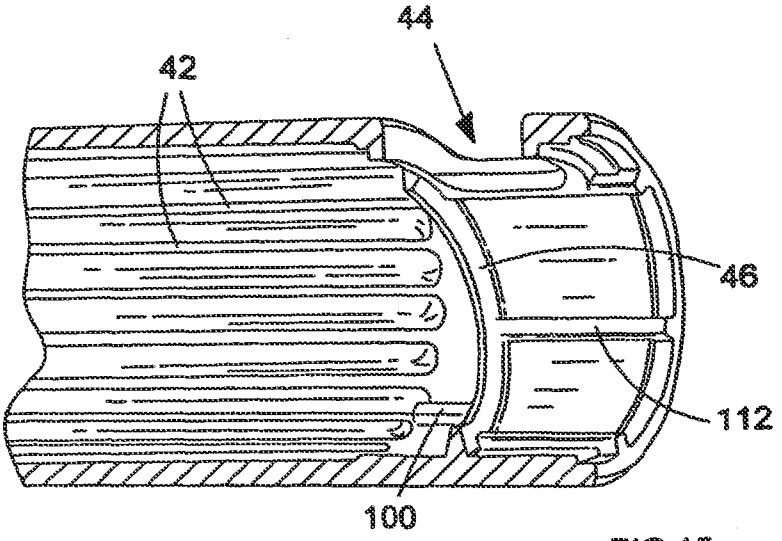

FIG.15

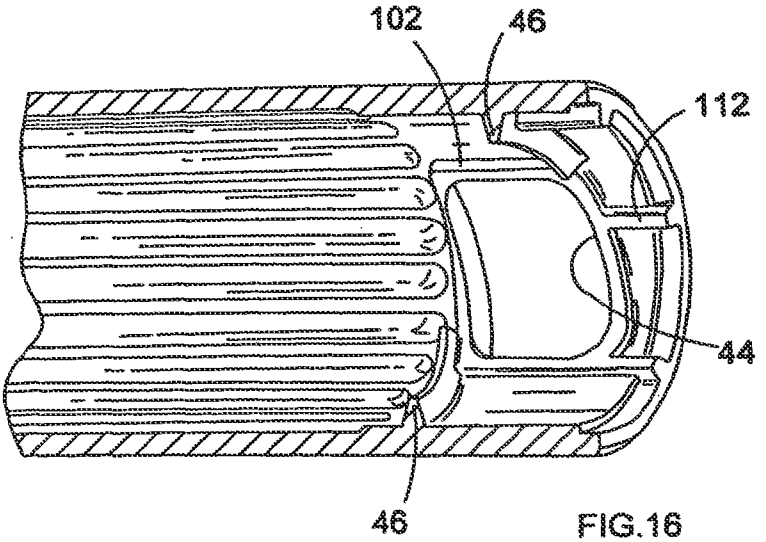

FIG.16

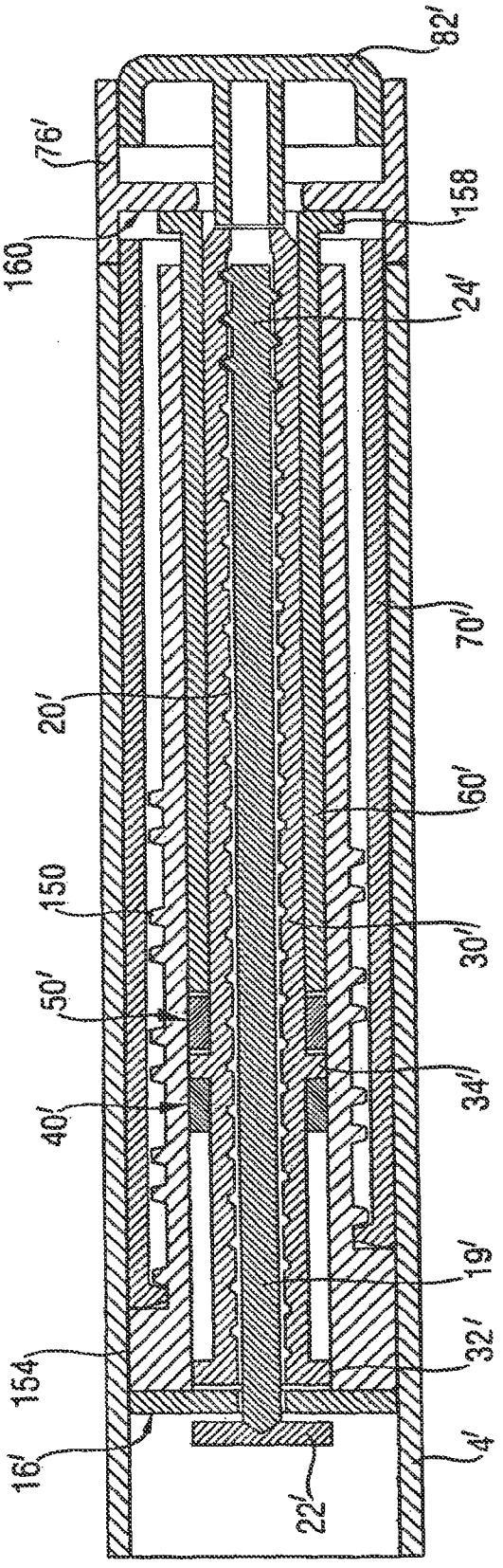

Fig. 17

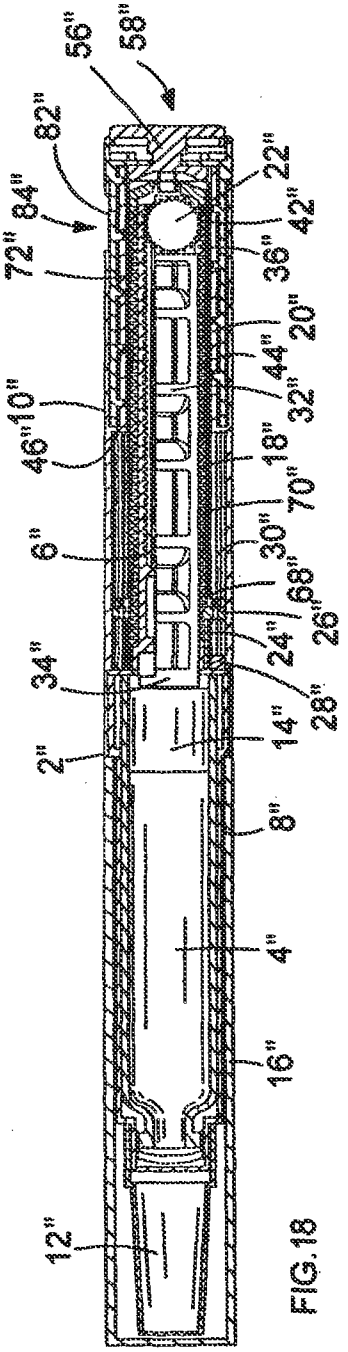
56"
58"
82"
84"
72"
22"
42"
36"
20"
44"
32"
10"
46"
18"
70"
30"
6"
68"
26"
24"
34"
28"
14"
2"
8"
4"
16"
12"

FIG. 18

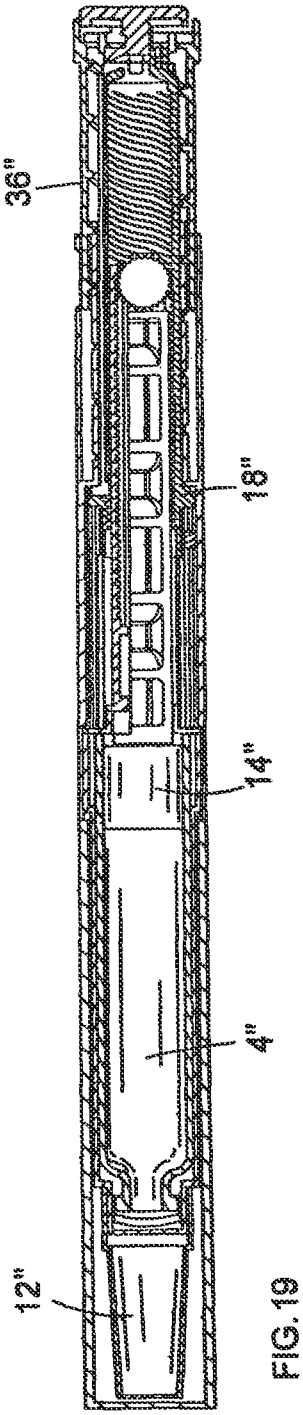
36"
18"
14"
4"
12"

FIG. 19

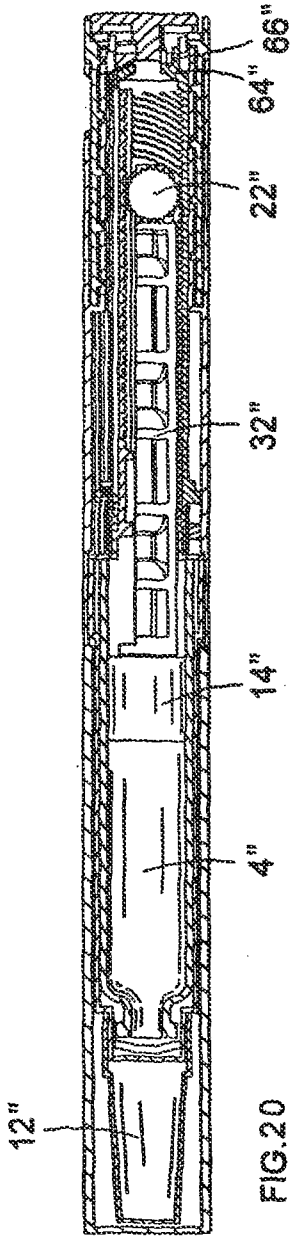

FIG.20

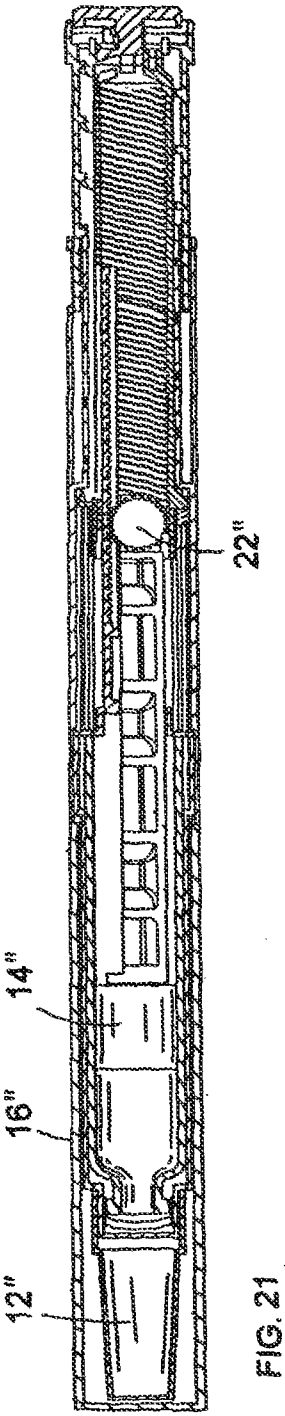

FIG. 21

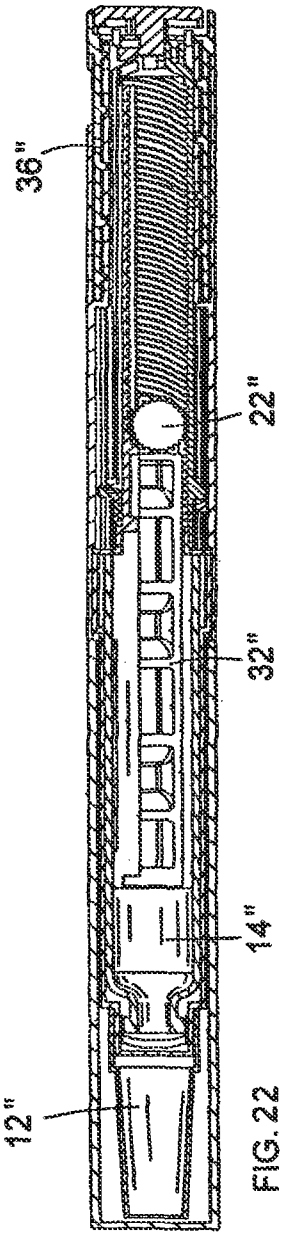

FIG. 22

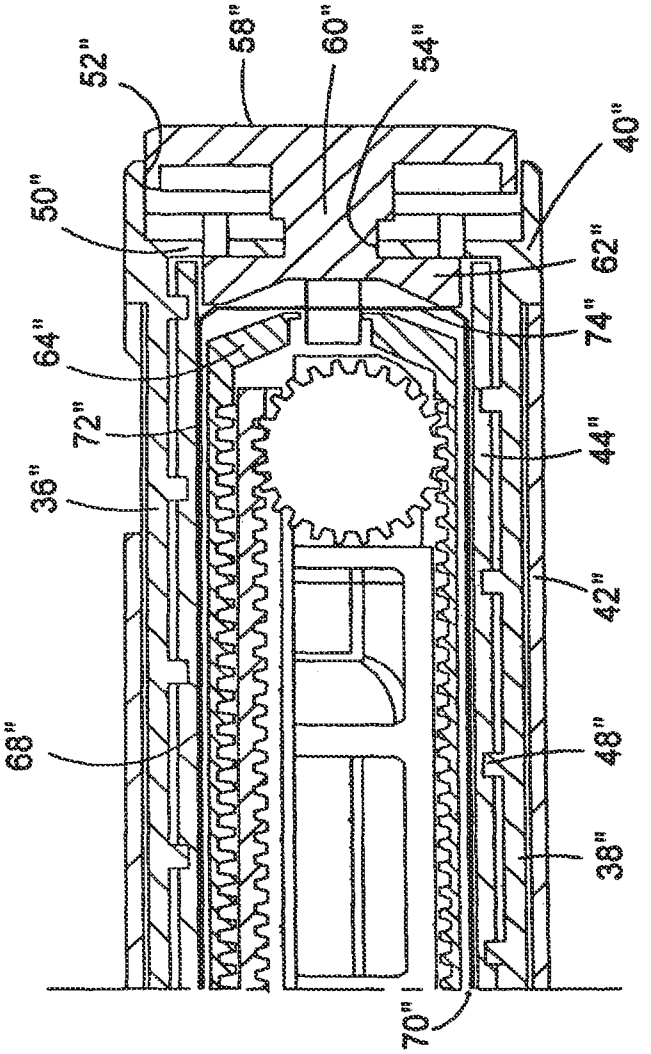

FIG. 23

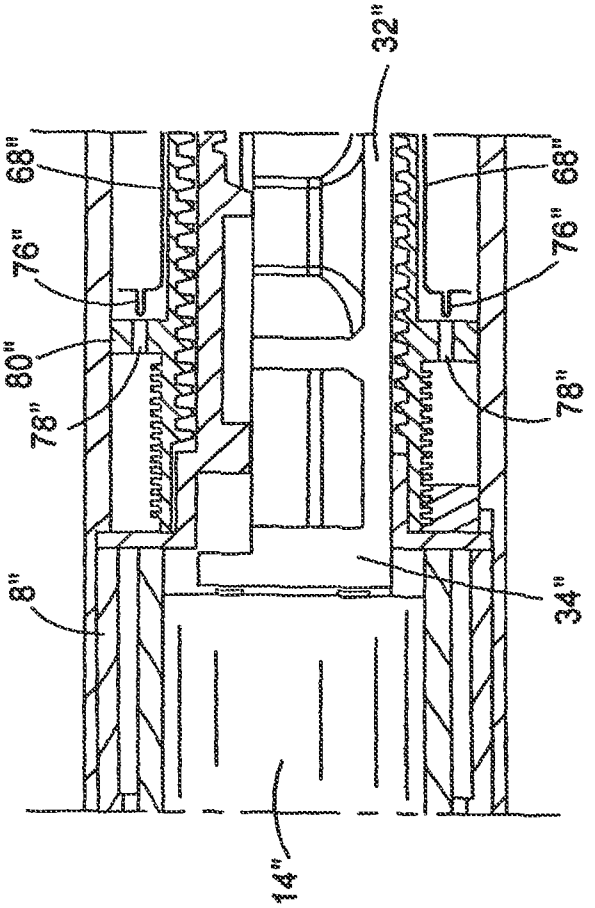

FIG. 24

DRIVE MECHANISMS SUITABLE FOR USE IN DRUG DELIVERY DEVICES

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 11/520,598, filed Sep. 14, 2009, now U.S. Pat. No. 7,935,088, which is a continuation application of U.S. patent application Ser. No. 10/790,866, filed Mar. 3, 2004, now abandoned, that claims priority to GB 0301822.0 filed Mar. 3, 2003, the entire contents of which are incorporated herein by reference.

TECHNICAL FIELD

The present invention relates to drive mechanisms suitable for use in drug delivery devices, in particular pen-type injectors, having dosage setting means, enabling the administration of medicinal products from a multi-dose cartridge. In particular, the present invention relates to such drug delivery devices where a user may set the dose.

BACKGROUND

Such drug delivery devices have application where regular injection by persons without formal medical training occurs, i.e., patients. This is increasingly common amongst those having diabetes where self-treatment enables such persons to conduct effective management of their diabetes.

These circumstances set a number of requirements for drug delivery devices of this kind. The device must be robust in construction, yet easy to use in terms of the manipulation of the parts, understanding by a user of its operation and the delivery of the required dose of medicament. Dose setting must be easy and unambiguous. In the case of those with diabetes, many users will be physically infirm and may also have impaired vision requiring the drive mechanism to have low dispensing force and an easy to read dose setting display. Where the device is to be disposable rather than reusable, the device should be cheap to manufacture and easy to dispose of (preferably being suitable for recycling). To meet these requirements the number of parts required to assemble the device and the number of material types the device is made from need to be kept to a minimum.

User operated drug delivery devices are well known within the medical field.

In U.S. Pat. No. 5,304,152 a dispensing device is disclosed which has a body length to plunger length ratio of about 1:1 in order to allow the dispensing of relatively large doses. Whilst this device provides many improvements over the prior art the easy correction of a set overdose remains unresolved without either dispensing the set amount of fluid or dismantling the cartridge.

WO 9938554 A2 teaches an injection syringe for apportioning set doses of a medicine from a cartridge wherein a drive mechanism comprising a unidirectional coupling (i.e., a ratchet) is disclosed which allows correction of a set overdose without dispensing the set amount of fluid or requiring the dismantling of the cartridge.

Surprisingly it was found that the drive mechanism according to instant invention without having a unidirectional coupling provides a valuable technical alternative for drive mechanisms, wherein reduced force is needed to actuate the mechanism. This is achieved by the introduction of a clutch means as defined by instant invention. The drive mechanism according to instant invention further provides the advantage of intuitive and easy to use correction of a set dose.

SUMMARY

According to a first aspect of the present invention, a drive mechanism for use in a drug delivery device is provided comprising:

- a housing having a helical thread;
- a dose dial sleeve having a helical thread engaged with the helical thread of the said housing;
- a drive sleeve releasably connected to the said dose dial sleeve;
- and a clutch means located between the dose dial sleeve and the drive sleeve;
- characterized in that,
  - a) when the dose dial sleeve and the drive sleeve are coupled, the dose dial sleeve and the drive sleeve are allowed to rotate with respect to the housing; and
  - b) when the dose dial sleeve and the drive sleeve are de-coupled, rotation of the dose dial sleeve with respect to the housing is allowed, whilst rotation of the drive sleeve with respect to the housing is not allowed, whereby axial movement of the drive sleeve is allowed so that a force is transferred in the longitudinal direction to the proximal end of the drug delivery device.

In a preferred embodiment of the drive mechanism of instant invention the said drive mechanism further comprises a piston rod adapted to operate through the housing and transfer the said force in the said longitudinal direction to the proximal end of the drug delivery device.

In another preferred embodiment of the drive mechanism of instant invention the said dose dial sleeve further comprises a helical thread, which has the same lead as the lead of the helical thread of the said drive sleeve.

In a more specific embodiment of instant invention, the drive mechanism further comprises a nut, which is rotatable with respect to the drive sleeve and axially displaceable but not rotatable with respect to the housing.

The term "drug delivery device" according to instant invention shall mean a single-dose or multi-dose, disposable or re-useable device designed to dispense a selected dose of a medicinal product, preferably multiple selected doses, e.g. insulin, growth hormones, low molecular weight heparins, and their analogues and/or derivatives etc. Said device may be of any shape, e.g. compact or pen-type. Dose delivery may be provided through a mechanical (optionally manual) or electrical drive mechanism or stored energy drive mechanism, such as a spring, etc. Dose selection may be provided through a manual mechanism or electronic mechanism. Additionally, said device may contain components designed to monitor physiological properties such as blood glucose levels, etc. Furthermore, the said device may comprise a needle or may be needle-free. In particular, the term "drug delivery device" shall mean a disposable multi-dose pen-type device having mechanical and manual dose delivery and dose selection mechanisms, which is designed for regular use by persons without formal medical training such as patients. Preferably, the drug delivery device is of the injector-type.

The term "housing" according to instant invention shall preferably mean any exterior housing ("main housing", "body", "shell") or interior housing ("insert", "inner body") having a helical thread. The housing may be designed to enable the safe, correct, and comfortable handling of the drug delivery device or any of its mechanism. Usually, it is designed to house, fix, protect, guide, and/or engage with any

of the inner components of the drug delivery device (e.g., the drive mechanism, cartridge, plunger, piston rod) by limiting the exposure to contaminants, such as liquid, dust, dirt etc. In general, the housing may be unitary or a multipart component of tubular or non-tubular shape. Usually, the exterior housing serves to house a cartridge from which a number of doses of a medicinal product may by dispensed.

In a more specific embodiment of instant invention, the exterior housing is provided with a plurality of maximum dose stops adapted to be abutted by a radial stop provided on the dose dial sleeve. Preferably, at least one of the maximum dose stops comprises a radial stop located between a helical thread and spline means provided at a second end of the housing. Alternatively, at least one of the maximum dose stops comprises a part of a raised window portion provided at a second end of the housing.

The term "engaged" according to instant invention shall particularly mean the interlocking of two or more components of the drive mechanism/drug delivery device, e.g. a spline, thread, or meshed teeth connection, preferably the interlocking of helical threads of components ("threadedly engaged").

The term "helical thread" according to instant invention shall preferably mean a full or part thread, e.g., a cylindrical spiral rib/groove, located on the internal and/or external surface of a component of the drug delivery device, having an essentially triangular or square or rounded section designed to allow continuous free rotational and/or axial movement between components. Optionally, a thread may be further designed to prevent rotational or axial movement of certain components in one direction.

The term "dose dial sleeve" according to instant invention shall mean an essentially tubular component of essentially circular cross-section having either:

a) both an internal and external thread, or

b) an internal thread, or

c) an external thread.

Preferably, the dose dial sleeve according to instant invention comprises a helical thread having a lead, which is similar to, preferably the same as the lead of the helical thread of the drive sleeve. In yet another preferred embodiment the dose dial sleeve is designed to indicate a selected dose of a dispensable product. This may be achieved by use of markings, symbols, numerals, etc., e.g. printed on the external surface of the dose dial sleeve or an odometer, or the like.

In a more specific embodiment of instant invention, the dose dial sleeve is provided with a plurality of radially extending members adapted to about a corresponding plurality of radial stops provided at a second end of the housing.

The term "lead" according to instant invention shall preferably mean the axial distance a nut would advance in one complete revolution; preferably "lead" shall mean the axial distance through which a component having a helical thread, i.e. dose dial sleeve, drive sleeve, piston rod, etc., of the drive mechanism travels during one rotation. Therefore lead is a function of the pitch of the thread of the relevant component.

The term "pitch" according to instant invention shall preferably mean the distance between consecutive contours on a helical thread, measured parallel to the axis of the helical thread.

The term "drive sleeve" according to instant invention shall mean any essentially tubular component of essentially circular cross-section and which is further releasably connected to the dose dial sleeve. In a preferred embodiment the drive sleeve is further engaged with the piston rod.

In a more particular embodiment of instant invention, the drive sleeve is provided at a first end with first and second flanges with an intermediate helical thread between the first and second flanges, having a nut disposed between the first and second flanges and keyed to the housing by spline means. Optionally, a first radial stop may be provided on a second face of the nut and a second radial stop may be provided on a first face of the second flange.

The term "releasably connected" according to instant invention shall preferably mean that two components of instant mechanism or device are reversibly joined to each other, which allows coupling and decoupling, e.g. by means of a clutch.

The term "piston rod" according to instant invention shall mean a component adapted to operate through/within the housing, designed to translate axial movement through/within the drug delivery device, preferably from the drive sleeve to the piston, for the purpose of discharging/dispensing an injectable product. Said piston rod may be flexible or not. It may be a simple rod, a lead-screw, a rack and pinion system, a worm gear system, or the like. The "piston rod" shall further mean a component having a circular or non-circular cross-section. It may be made of any suitable material known by a person skilled in the art.

In a preferred embodiment, the piston rod comprises at least one, more preferably two, external and/or internal helical threads. In another preferred embodiment of the piston rod according to instant invention, a first helical thread is located at a first end and a second helical thread is located at a second end of the said piston rod, whereby the said threads may have the same or, preferably, opposite dispositions. In another preferred embodiment the piston rod of instant invention comprises threads having the same leads at the first and the second end.

In yet another preferred embodiment of instant invention the lead of the first helical thread of the piston rod shall be greater than the lead of the second helical thread. More preferred, the ratio of the leads of the helical threads of the said first and the second helical threads is 1:1.01 to 1:20, even more preferred 1:1.1 to 1:10. Preferably, one of the said threads is designed to engage with the drive sleeve.

Alternatively, in another preferred embodiment of the piston rod of instant invention, the piston rod is designed to have attached, optionally by means of a journal bearing, a toothed gear, and wherein said toothed gear is designed to mesh with the threads of the drive sleeve and the teeth of a toothed rack, whereby said toothed rack is fixed to the housing.

The term "first end" according to instant invention shall mean the proximal end. The proximal end of the device or a component of the device shall mean the end, which is closest to the dispensing end of the device.

The term "second end" according to instant invention shall mean the distal end. The distal end of the device or a component of the device shall mean the end, which is furthest away from the dispensing end of the device.

The term "clutch means" according to instant invention shall mean any means, which releasably connects the dose dial sleeve and the drive sleeve and which is designed to allow rotation of the dose dial sleeve and the drive sleeve with respect to the housing when the dose dial sleeve and the drive sleeve are coupled and, when both are de-coupled, allows rotation of the dose dial sleeve with respect to the housing, but does not allow rotation of the drive sleeve with respect to the housing and allows axial movement of the drive sleeve. Preferably, the clutch means releasably connects the drive sleeve to the housing. Accordingly, the term clutch means is any clutch engaging for the purpose of reversibly locking two

components in rotation, e.g., by use of axial forces to engage a set of face teeth (saw teeth, dog teeth, crown teeth) or any other suitable frictional faces.

In a more specific embodiment of instant invention, a second end of the clutch means is provided with a plurality of dog teeth adapted to engage with a second end of the dose dial sleeve.

In an alternative embodiment, the clutch means of instant invention is a locking spring, operable, e.g., by means of a dose dial button, between a first, relaxed position, in which the dose dial sleeve is locked with respect to rotation with the drive sleeve and a second, deformed position, in which the dose dial sleeve is locked with respect to rotation with the housing.

In still another embodiment of instant invention, the drive mechanism further comprises a clicker means, optionally disposed between the clutch means and spline means provided on the housing.

Optionally, the clicker means comprises a sleeve provided at a first end with a helically extending arm, a free end of the arm having a toothed member, and at a second end with a plurality of circumferentially directed saw teeth adapted to engage a corresponding plurality of circumferentially saw teeth provided on the clutch means. Alternatively, the clicker means comprises a sleeve provided at a first end with at least one helically extending arm and at least one spring member, a free end of the arm having a toothed member, and at a second end with a plurality of circumferentially directed saw teeth adapted to engage a corresponding plurality of circumferentially directed saw teeth provided on the clutch means.

In still another embodiment of the drive mechanism of the invention, the drive mechanism is provided with a first stop means, preferably in the form of an external flange on the dose dial sleeve, adapted to engage limiting means associated with the housing, preferably in the form of an internal flange in the housing, to limit the maximum dose which can be dialed. In yet another embodiment of the drive mechanism of the invention, the drive mechanism is further provided with a second stop means, preferably in the form of an external flange on the drive sleeve, adapted to engage limiting means, preferably in the form of a limiting nut keyed to the housing and mounted for rotation on an external threaded section of the drive sleeve, to provide an end of life stop.

A second aspect of instant invention provides an assembly for use in a drug delivery device comprising the drive mechanism according to instant invention.

A third aspect of the present invention provides a drug delivery device comprising the drive mechanism or the assembly according to instant invention.

A fourth aspect of the present invention provides a method of assembling a drug delivery device comprising the step of providing a drive mechanism or an assembly according to instant invention.

A fifth aspect of instant invention is the use of a drug delivery device according to instant invention for dispensing a medicinal product preferably dispensing a pharmaceutical formulation (e.g. solution, suspension etc.) comprising an active compound selected from the group consisting of insulin, growth hormone, low molecular weight heparin, their analogues and their derivatives.

BRIEF DESCRIPTION OF THE FIGURES

Without any limitation, the instant invention will be explained in greater detail below in connection with a preferred embodiment and with reference to the drawings in which:

FIG. **1** shows a sectional view of a first embodiment of the drug delivery device in accordance with the present invention in a first, cartridge full, position;

FIG. **2** shows a sectional view of the drug delivery device of FIG. **1** in a second, maximum first dose dialed, position;

FIG. **3** shows a sectional view of the drug delivery device of FIG. **1** in a third, maximum first dose dispensed, position;

FIG. **4** shows a sectional view of the drug delivery device of FIG. **1** in a fourth, final dose dialed, position;

FIG. **5** shows a sectional view of the drug delivery device of FIG. **1** in a fifth, final dose dispensed, position;

FIG. **6** shows a cut-away view of a first detail of the drug delivery device of FIG. **1**;

FIG. **7** shows a partially cut-away view of a second detail of the drug delivery device of FIG. **1**;

FIG. **8** shows a partially cut-away view of a third detail of the drug delivery device of FIG. **1**;

FIG. **9** shows the relative movement of parts of the drug delivery device shown in FIG. **1** during dialing up of a dose;

FIG. **10** shows the relative movement of parts of the drug delivery device shown in FIG. **1** during dialing down of a dose;

FIG. **11** shows the relative movement of parts of the drug delivery device shown in FIG. **1** during dispensing of a dose;

FIG. **12** shows a partially cut-away view of the drug delivery device of FIG. **1** in the second, maximum first dose dialed, position;

FIG. **13** shows a partially cut-away view of the drug delivery device of FIG. **1** in the fourth, final dose dialed, position;

FIG. **14** shows a partially cut-away view of the drug delivery device of FIG. **1** in one of the first, third or fifth positions;

FIG. **15** shows a cut-away view of a first part of a main housing of the drug delivery device of FIG. **1**; and

FIG. **16** shows a cut-away view of a second part of the main housing of the drug delivery device of FIG. **1**;

FIG. **17** shows a sectional view of a second embodiment of the drive mechanism according to instant invention in a first, cartridge full, position.

FIG. **18** shows a sectional side view of a third embodiment of the drug delivery device in accordance with the present invention in a first, cartridge full, position;

FIG. **19** shows a sectional side view of the drug delivery device of FIG. **18** in a second, maximum first dose dialed, position;

FIG. **20** shows a sectional side view of the drug delivery device of FIG. **18** in a third, maximum first dose dispensed, position;

FIG. **21** shows a sectional side view of the drug delivery device of FIG. **18** in a fourth, final dose dialed, position;

FIG. **22** shows a sectional side view of the drug delivery device of FIG. **18** in a fifth, final dose dispensed, position;

FIG. **23** shows a fragment of the drug delivery device of FIG. **18** in a larger scale and

FIG. **24** shows a further fragment of the drug delivery device of FIG. **18** in a larger scale.

DETAILED DESCRIPTION

Example 1

Referring first to FIGS. **1** to **5**, there is shown a drug delivery device in accordance with the present invention in a number of positions.

The drug delivery device comprises a housing having a first cartridge retaining part **2**, and second main (exterior) housing part **4**. A first end of the cartridge retaining means **2** and a second end of the main housing **4** are secured together by

retaining features **6**. In the illustrated embodiment, the cartridge retaining means **2** is secured within the second end of the main housing **4**.

A cartridge **8** from which a number of doses of a medicinal product may be dispensed is provided in the cartridge retaining part **2**. A piston **10** is retained in a first end of the cartridge **8**.

A removable cap **12** is releasably retained over a second end of the cartridge retaining part **2**. In use the removable cap **12** can be replaced by a user with a suitable needle unit (not shown). A replaceable cap **14** is used to cover the cartridge retaining part **2** extending from the main housing **4**. Preferably, the outer dimensions of the replaceable cap **14** are similar or identical to the outer dimensions of the main housing **4** to provide the impression of a unitary whole when the replaceable cap **14** is in position covering the cartridge retaining part **2**.

In the illustrated embodiment, an insert **16** is provided at a first end of the main housing **4**. The insert **16** is secured against rotational or longitudinal motion. The insert **16** is provided with a threaded circular opening **18** extending therethrough. Alternatively, the insert may be formed integrally with the main housing **4** having the form of a radially inwardly directed flange having an internal thread.

A first thread **19** extends from a first end of a piston rod **20**. The piston rod **20** is of generally circular section. The first end of the piston rod **20** extends through the threaded opening **18** in the insert **16**. A pressure foot **22** is located at the first end of the piston rod **20**. The pressure foot **22** is disposed to abut a second end of the cartridge piston **10**. A second thread **24** extends from a second end of the piston rod **20**. In the illustrated embodiment the second thread **24** comprises a series of part threads rather than a complete thread. The illustrated embodiment is easier to manufacture and helps to reduce the overall force required for a user to actuate the device when dispensing the medicinal product.

The first thread **19** and the second thread **24** are oppositely disposed. The second end of the piston rod **20** is provided with a receiving recess **26**.

A drive sleeve **30** extends about the piston rod **20**. The drive sleeve **30** is generally cylindrical. The drive sleeve **30** is provided at a first end with a first radially extending flange **32**. A second radially extending flange **34** is provided spaced a distance along the drive sleeve **30** from the first flange **32**. An intermediate thread **36** is provided on an outer part of the drive sleeve **30** extending between the first flange **32** and the second flange **34**. A helical groove (thread) **38** extends along the internal surface of the drive sleeve **30**. The second thread **24** of the piston rod **20** is adapted to work within the helical groove **38**.

A first end of the first flange **32** is adapted to conform to a second side of the insert **16**.

A nut **40** is located between the drive sleeve **30** and the main housing **4**, disposed between the first flange **32** and the second flange **34**. In the illustrated embodiment the nut **40** is a half-nut. This assists in the assembly of the device. The nut **40** has an internal thread matching the intermediate thread **36**. The outer surface of the nut **40** and an internal surface of the main housing **4** are keyed together by splines **42** (FIGS. **10**, **11**, **15** and **16**) to prevent relative rotation between the nut **40** and the main housing **4**, while allowing relative longitudinal movement therebetween.

A shoulder **37** is formed between a second end of the drive sleeve **30** and an extension **47** provided at the second end of the drive sleeve **30**. The extension **47** has reduced inner and outer diameters in comparison to the remainder of the drive sleeve **30**. A second end of the extension **47** is provided with a radially outwardly directed flange **39**.

A clicker **50** and a clutch **60** are disposed about the drive sleeve **30**, between the drive sleeve **30** and a dose dial sleeve **70** (described below).

The clicker **50** is located adjacent the second flange **34** of the drive sleeve **30**. The clicker **50** is generally cylindrical and is provided at a first end with a flexible helically extending arm **52** (FIG. **6**). A free end of the arm **52** is provided with a radially directed toothed member **54**. A second end of the clicker **50** is provided with a series of circumferentially directed saw teeth **56** (FIG. **7**). Each saw tooth comprises a longitudinally directed surface and an inclined surface.

In an alternative embodiment (not shown) the clicker further includes at least one spring member. The at least one spring member assists in the resetting of the clutch **60** following dispense.

The clutch **60** is located adjacent the second end of the drive sleeve **30**. The clutch **60** is generally cylindrical and is provided at a first end with a series of circumferentially directed saw teeth **66** (FIG. **7**). Each saw tooth comprises a longitudinally directed surface and an inclined surface. Towards the second end **64** of the clutch **60** there is located a radially inwardly directed flange **62**. The flange **62** of the clutch **60** is disposed between the shoulder **37** of the drive sleeve **30** and the radially outwardly directed flange **39** of the extension **47**. The second end of the clutch **60** is provided with a plurality of dog teeth **65** (FIG. **8**). The clutch **60** is keyed to the drive sleeve **30** by way of splines (not shown) to prevent relative rotation between the clutch **60** and the drive sleeve **30**.

In the illustrated embodiment, the clicker **50** and the clutch. **60** each extend approximately half the length of the drive sleeve **30**. However, it will be understood that other arrangements regarding the relative lengths of these parts are possible.

The clicker **50** and the clutch **60** are engaged as shown in FIG. **7**.

A dose dial sleeve **70** is provided outside of the clicker **50** and clutch **60** and radially inward of the main housing **4**. A helical groove **74** is provided about an outer surface of the dose dial sleeve **70**.

The main housing **4** is provided with a window **44** through which a part of the outer surface of the dose dial sleeve may be seen. The main housing **4** is further provided with a helical rib (thread) **46**, adapted to be seated in the helical groove (thread) **74** on the outer surface of the dose dial sleeve **70**. The helical rib **46** extends for a single sweep of the inner surface of the main housing **4**. A first stop **100** is provided between the splines **42** and the helical rib **46** (FIG. **15**). A second stop **102**, disposed at an angle of 180° to the first stop **100** is formed by a frame surrounding the window **44** in the main housing **4** (FIG. **16**).

Conveniently, a visual indication of the dose that may be dialed, for example reference numerals (not shown), is provided on the outer surface of the dose dial sleeve **70**. The window **44** conveniently only, allows to be viewed a visual indication of the dose currently dialed.

A second end of the dose dial sleeve **70** is provided with an inwardly directed flange in the form of a number of radially extending members **75**. A dose dial grip **76** is disposed about an outer surface of the second end of the dose dial sleeve **70**. An outer diameter of the dose dial grip **76** preferably corresponds to the outer diameter of the main housing **4**. The dose dial grip **76** is secured to the dose dial sleeve **70** to prevent relative movement therebetween. The dose dial grip **76** is

provided with a central opening **78**. An annular recess **80** located in the second end of the dose dial grip **76** extends around the opening **78**.

A button **82** of generally 'T' section is provided at a second end of the device. A stem **84** of the button **82** may extend through the opening **78** in the dose dial grip **76**, through the inner diameter of the extension **47** of the drive sleeve **30** and into the receiving recess **26** of the piston rod **20**. The stem **84** is retained for limited axial movement in the drive sleeve **30** and against rotation with respect thereto. A head **85** of the button **82** is generally circular. A skirt **86** depends from a periphery of the head **85**. The skirt **86** is adapted to be seated in the annular recess **80** of the dose dial grip **76**.

Operation of the drug delivery device in accordance with the present invention will now be described. In FIGS. **9**, **10** and **11** arrows A, B, C, D, E, F and G represent the respective movements of the button **82**, the dose dial grip **76**, the dose dial sleeve **70**, the drive sleeve **30**, the clutch **60**, the clicker **50** and the nut **40**.

To dial a dose (FIG. **9**) a user rotates the dose dial grip **76** (arrow B). With the clicker **50** and clutch **60** engaged, the drive sleeve **30**, the clicker **50**, the clutch **60** and the dose dial sleeve **70** rotate with the dose dial grip **76**.

Audible and tactile feedback of the dose being dialed is provided by the clicker **50** and the clutch **60**. Torque is transmitted through the saw teeth **56**,**66** between the clicker **50** and the clutch **60**. The flexible arm **52** deforms and drags the toothed member **54** over the splines **42** to produce a click. Preferably, the splines **42** are disposed such that each click corresponds to a conventional unit dose, or the like.

The helical groove **74** on the dose dial sleeve **70** and the helical groove **38** in the drive sleeve **30** have the same lead. This allows the dose dial sleeve **70** (arrow C) to extend from the main housing **4** and the drive sleeve **30** (arrow D) to climb the piston rod **20** at the same rate. At the limit of travel, a radial stop **104** (FIG. **12**) on the dose dial sleeve **70** engages either the first stop **100** or the second stop **102** provided on the main housing **4** to prevent further movement. Rotation of the piston rod **20** is prevented due to the opposing directions of the overhauled and driven threads on the piston rod **20**.

The nut **40**, keyed to the main housing **4**, is advanced along the intermediate thread **36** by the rotation of the drive sleeve **30** (arrow D). When the final dose dispensed position (FIGS. **4**, **5** and **13**) is reached, a radial stop **106** formed on a second surface of the nut **40** abuts a radial stop **108** on a first surface of the second flange **34** of the drive sleeve **30**, preventing both the nut **40** and the drive sleeve **30** from rotating further.

In an alternative embodiment (not shown) a first surface of the nut **40** is provided with a radial stop for abutment with a radial stop provided on a second surface of the first flange **32**. This aids location of the nut **40** at the cartridge full position during assembly of the drug delivery device.

Should a user inadvertently dial beyond the desired dosage, the drug delivery device allows the dosage to be dialed down without dispense of medicinal product from the cartridge (FIG. **10**). The dose dial grip **76** is counter rotated (arrow B). This causes the system to act in reverse. The flexible arm **52** preventing the clicker **50** from rotating. The torque transmitted through the clutch **60** causes the saw teeth **56**,**66** to ride over one another to create the clicks corresponding to dialed dose reduction. Preferably the saw teeth **56**,**66** are so disposed that the circumferential extent of each saw tooth corresponds to a unit dose.

When the desired dose has been dialed, the user may then dispense this dose by depressing the button **82** (FIG. **11**). This displaces the clutch **60** axially with respect to the dose dial sleeve **70** causing the dog teeth **65** to disengage. However the clutch **60** remains keyed in rotation to the drive sleeve **30**. The dose dial sleeve **70** and associated dose dial grip **76** are now free to rotate (guided by the helical rib **46** located in helical groove **74**).

The axial movement deforms the flexible arm **52** of the clicker **50** to ensure the saw teeth **56**,**66** cannot be overhauled during dispense. This prevents the drive sleeve **30** from rotating with respect to the main housing **4** though it is still free to move axially with respect thereto. This deformation is subsequently used to urge the clicker **50**, and the clutch **60**, back along the drive sleeve **30** to restore the connection between the clutch **60** and the dose dial sleeve **70** when pressure is removed from the button **82**.

The longitudinal axial movement of the drive sleeve **30** causes the piston rod **20** to rotate though the opening **18** in the insert **16**, thereby to advance the piston **10** in the cartridge **8**. Once the dialed dose has been dispensed, the dose dial sleeve **70** is prevented from further rotation by contact of a plurality of members **110** (FIG. **14**) extending from the dose dial grip **76** with a corresponding plurality of stops **112** formed in the main housing **4** (FIGS. **15** and **16**). In the illustrated embodiment, the members **110** extend axially from the dose dial grip **76** and have an inclined end surface. The zero dose position is determined by the abutment of one of the axially extending edges of the members **110** with a corresponding stop **112**.

Example 2

In another embodiment of the invention (FIG. **17**) there is seen a drive mechanism comprising a second main housing **4'** having a first end and a second end. A cartridge, containing medicinal product, can be mounted to the first end of the second main housing **4'** and retained by any suitable means. The cartridge and its retaining means are not shown in the illustrated embodiment. The cartridge may contain a number of doses of a medicinal product and also typically contains a displaceable piston. Displacement of the piston causes the medicinal product to be expelled from the cartridge via a needle (also not shown).

In the illustrated embodiment, an insert **16'** is provided within the main housing **4'**. The insert **16'** is secured against rotational and axial motion with respect to the second main housing **4'**. The insert **16'** is provided with a threaded circular opening extending therethrough. Alternatively, the insert may be formed integrally with the second main housing **4'**.

An internal housing **154** is also provided within the second main housing **4'**. The internal housing **154** is secured against rotational and axial motion with respect to the second main housing **4'**. The internal housing **154** is provided with a circular opening extending through its length in which a series of longitudinally directed splines are formed. A helical thread **150** extends along the outer cylindrical surface of the internal housing **154**. Alternatively, the internal housing may be formed integrally with the second main housing **4'** and/or with the insert **16'**.

A first thread **19'** extends from a first end of a piston rod **20'**. The piston rod **20'** is of generally circular section. The first end of the piston rod **20'** extends through the threaded opening in the insert **16'** and the first thread **19'** of the piston rod **20'** is engaged with the thread of the insert **16'**. A pressure foot **22'** is located at the first end of the piston rod **20'**. The pressure foot **22'** is disposed to abut a cartridge piston (not shown). A second thread **24'** extends from a second end of the piston rod **20'**. The first thread **19'** and the second thread **24'** are oppositely disposed.

A drive sleeve **30'** extends about the piston rod **20'**. The drive sleeve **30'** is generally cylindrical. The drive sleeve **30'** is

provided at a first end with a first radially extending flange **32'**. A second radially extending flange **34'** is provided, spaced a distance along the drive sleeve **30'** from the first flange **32'**. An external helical thread (not shown) is provided on the outer part of the drive sleeve **30'** extending between the first flange **32'** and the second flange **34'**. An internal helical thread extends along the internal surface of the drive sleeve **30'**. The second thread **24'** of the piston rod **20'** is engaged with the internal helical thread of the drive sleeve **30'**.

A nut **40'** is located between the drive sleeve **30'** and the internal housing **154**, disposed between the first flange **32'** and the second flange **34'** of the drive sleeve **30'**. The nut **40'** can be either a 'half-nut' or a 'full-nut'. The nut **40'** has an internal thread that is engaged with the external helical thread of the drive sleeve **30'**. The outer surface of the nut **40'** and an internal surface of the internal housing **154** are keyed together by means of longitudinally directed splines to prevent relative rotation between the nut **40'** and the internal housing **154**, while allowing relative longitudinal movement therebetween.

A clicker **50'** and a clutch **60'** are disposed about the drive sleeve **30'**, between the drive sleeve **30'** and the internal housing **154**.

The clicker **50'** is located adjacent the second flange **34'** of the drive sleeve **30'**. The clicker **50'** includes at least one spring member (not shown). The clicker **50'** also includes a set of teeth (not shown) having a triangular profile disposed towards the second end of the drive mechanism. When compressed, the at least one spring member of the clicker **50'** applies an axial force between the flange **34'** of the drive sleeve **30'** and the clutch **60'**. The outer surface of the clicker **50'** and an internal surface of the internal housing **154** are keyed together by means of longitudinally directed splines to prevent relative rotation between the clicker **50'** and the internal housing **154**, while allowing relative longitudinal movement therebetween.

The clutch **60'** is located adjacent the second end of the drive sleeve **30'**. The clutch **60'** is generally cylindrical and is provided at its' first end with a plurality of teeth of triangular profile disposed about the circumference (not shown), that act upon the teeth of the clicker **50'**. Towards the second end of the clutch **60'** there is located a shoulder **158**. The shoulder **158** of the clutch **60'** is disposed between the internal housing **154** and a radially inwardly directed flange of the dose dial grip **76'** (described below). The shoulder **158** of the clutch **60'** is provided with a plurality of dog teeth (not shown) extending in the direction of the second end of the drive mechanism. The clutch **60'** is keyed to the drive sleeve **30'** by way of splines (not shown) to prevent relative rotation between the clutch **60'** and the drive sleeve **30'**.

A dose dial sleeve **70'** is provided outside of the internal housing **154** and radially inward from the second main housing **4'**. A helical thread is provided on an inner surface of the dose dial sleeve **70'**. The helical thread of the dose dial sleeve **70'** is engaged with the helical thread **150** of the internal housing **154**.

The second main housing **4'** is provided with a window (not shown) through which part of the outer surface of the dose dial sleeve **70'** may be viewed. Conveniently, a visual indication of the dose that may be dialed, for example reference numerals (not shown), is provided on the outer surface of the dose dial sleeve **70'**. Conveniently, the window of the second main housing **4'** allows only the dose that is currently dialed to be viewed.

A dose dial grip **76'** is located towards the second end of the drive mechanism. The dose dial grip **76'** is secured against rotational and axial motion within respect to the dose dial sleeve **70'**. The dose dial grip **76'** is provided with a radially inwardly directed flange **160**. The radially inwardly directed flange **160** of the dose dial grip **76'** is provided with a plurality of dog teeth (not shown) extending in the direction of the first end of the drive mechanism to abut the dog teeth of the clutch **60'**. Coupling and decoupling of the dog teeth of the dose dial grip **76'** with the dog teeth of the clutch **60'** provides a releasable clutch between the dose dial grip **76'** and the clutch **60'**.

A button **82'** of generally 'T' shaped cross-section is provided at a second end of the drive mechanism. A cylindrical feature of the button **82'** extends towards the first end of the drive mechanism, through an opening in the dose dial grip **76'** and into a recess in the drive sleeve **30'**. The cylindrical feature of the button **82'** is retained for limited axial movement in the drive sleeve **30'** and against rotation with respect thereto. The cylindrical feature of the button **82'** has lugs extending radially (not shown) that abut the second surface of the shoulder **158** of the clutch **60'**. The second end of the button **82'** is generally circular and has a cylindrical skirt about its' periphery that descends towards the first end of the drive mechanism. The skirt of the button **82'** is located radially inward from the dose dial grip **76'**.

Operation of the drive mechanism in accordance with the present invention will now be described.

To dial a dose, a user rotates the dose dial grip **76'**. The spring member of the clicker **50'** applies an axial force to the clutch **60'** in the direction of the second end of the drive mechanism. The force exerted by the spring member of the clicker **50'** couples the dog teeth of the clutch **60'** to the dog teeth of the dose dial grip **76'** for rotation. As the dose dial grip **76'** is rotated, the associated dose dial sleeve **70'**, the drive sleeve **30'** and the clutch **60'** all rotate in unison.

Audible and tactile feedback of the dose being dialed is provided by the clicker **50'** and the clutch **60'**. As the clutch **60'** is rotated, torque is transmitted from the teeth at the first end of the clutch **60'** and the teeth of the clicker **50'**. The clicker **50'** cannot rotate with respect to the internal housing **154**, so the at least one spring member of the clicker **50'** deforms allowing the teeth of the clutch **60'** to jump over the teeth of the clicker **50'** producing an audible and tactile 'click'. Preferably, the teeth of the clicker **50'** and the teeth of the clutch **60'** are disposed such that each 'click' corresponds to a conventional unit of the medicinal product, or the like.

The helical thread of the dose dial sleeve **70'** and the internal helical thread of the drive sleeve **30'** have the same lead. This allows the dose dial sleeve **70'** to advance along the thread **150** of the internal housing **154** at the same rate as the drive sleeve **30'** advances along the second thread **24'** of the piston rod **20'**. Rotation of the piston rod **20'** is prevented due to the opposing direction of the first thread **19'** and the second thread **24'** of the piston rod **20'**. The first thread **19'** of the piston rod **20'** is engaged with the thread of the insert **16'** and so the piston rod **20'** does not move with respect to the second main housing **4'** while a dose is dialed.

The nut **40'**, keyed to the internal housing **154**, is advanced along the external thread of the drive sleeve **30'** by the rotation of the drive sleeve **30'**. When a user has dialed a quantity of medicinal product that is equivalent to the deliverable volume of the cartridge, the nut **40'** reaches a position where it abuts the second flange **34'** of the drive sleeve **30'**. A radial stop formed on the second surface of the nut **40'** contacts a radial stop on the first surface of the second flange **34'** of the drive sleeve **30'**, preventing both the nut **40'** and the drive sleeve **30'** from being rotated further.

Should a user inadvertently dial a quantity greater than the desired dosage, the drive mechanism allows the dosage to be corrected without dispense of medicinal product from the

cartridge. The dose dial grip **76'** is counter-rotated. This causes the system to act in reverse. The torque transmitted through the clutch **60'** causes the teeth at the first end of the clutch **60'** to ride over the teeth of the clicker **50'** to create the clicks corresponding to the dialed dose reduction.

When the desired dose has been dialed, the user may then dispense this dose by depressing the button **82'** in the direction of the first end of the drive mechanism. The lugs of the button **82'** apply pressure to the second surface of the shoulder **158** of the clutch **60'**, displacing the clutch **60'** axially with respect to the dose dial grip **76'**. This causes the dog teeth on the shoulder **158** of the clutch **60'** to disengage from the dog teeth of the dose dial grip **76'**. However, the clutch **60'** remains keyed in rotation to the drive sleeve **30'**. The dose dial grip **76'** and associated dose dial sleeve **70'** are now free to rotate (guided by the helical thread **150** of the internal housing **154**).

The axial movement of the clutch **60'** deforms the spring member of the clicker **50'** and couples the teeth at the first end of the clutch **60'** to the teeth of the clicker **50'** preventing relative rotation therebetween. This prevents the drive sleeve **30'** from rotating with respect to the internal housing **154**, though it is still free to move axially with respect thereto.

Pressure applied to the button **82'** thus causes the dose dial grip **76'** and the associated dose dial sleeve **70'** to rotate into the second main housing **4'**. Under this pressure the clutch **60'**, the clicker **50'** and the drive sleeve **30'** are moved axially in the direction of the first end of the drive mechanism, but they do not rotate. The axial movement of the drive sleeve **30'** causes the piston rod **20'** to rotate though the threaded opening in the insert **16'**, thereby to advance the pressure foot **22'**. This applies force to the piston, causing the medicinal product to be expelled from the cartridge. The selected dose is delivered when the dose dial grip **76'** returns to a position where it abuts the second main housing **4'**.

When pressure is removed from the button **82'**, the deformation of the spring member of the clicker **50'** is used to urge the clutch **60'** back along the drive sleeve **30'** to re-couple the dog teeth on the shoulder **158** of the clutch **60'** with the dog teeth on the dose dial grip **76'**. The drive mechanism is thus reset in preparation to dial a subsequent dose.

Example 3

Referring to FIGS. **18** to **22** there may be seen a drug delivery device in accordance with the present invention. The drug delivery device comprises a two-part housing **2"** within which are located a cartridge **4"** containing a medicinal product, means for setting or selecting the dose of medicinal product to be expelled and means for expelling the selected dose of medicinal product. The housing **2"** is generally cylindrical in shape and houses a rack **6"** to be described in more detail below. The cartridge **4"** is located within a first part **8"** of the housing **2"**. The dose setting means and the means for expelling the selected dose of medicinal product are retained, that is held, within a second part **10"** of the housing **2"**. The first part **8"** of the housing **2"** and the second part **10"** of the housing **2"** may be secured together by any suitable means.

The cartridge **4"** may be secured in position in the first part **8"** of the housing **2"** by any suitable means. A needle unit may be secured to a first end of the cartridge **4"**. A temporary covering **12"** is shown in this position in the Figures. The cartridge **4"** further comprises a displaceable piston **14"**. Advancing the piston **10"** towards the first end of the cartridge **4"** causes the medicinal product to be expelled from the cartridge **4"** through the needle unit. A cap **16"** is provided to cover the needle unit when the drug delivery device is not in use. The cap **16"** may be releasably secured to the 1 housing **2"** by any suitable means.

The dose setting means and the means for expelling the selected dose of medicinal product will now be described in more detail. The rack **6"** is located within a drive sleeve **18"** located within the housing **2"** and is fixed both axially and rotationally with respect to the housing **2"** by any suitable means. The drive sleeve **18"** comprises an internally threaded portion **20"**, which extends along substantially the entire internal surface of the sleeve. An internal toothed gear **22"** is located within the drive sleeve **18"** and has helical teeth which match the pitch of the internal thread of the drive sleeve **18"**. The internal thread of the drive sleeve **18"** is a multistart thread with a lead which is the same as the lead of the helical thread of the dose dial sleeve, which will be described later. The drive sleeve **18"** terminates in an externally threaded section **24"** which extends from an end of the sleeve as far as an external circumferential flange **26"** which projects from the drive sleeve **18"**. A limiting nut **28"** is mounted for rotation on the externally threaded section **24"** of the sleeve **14"**. The limiting nut **28"** is keyed to the housing **2"** by means of a plurality of longitudinally extending splines **30"** which extend along the internal surface of the first portion **8"** of the housing **2"**. In the illustrated embodiment, the limiting nut **28"** is shown as a half-nut, but a full nut could be used.

A piston rod **32"** is provided extending along the length of the rack **6"** and through a hole in the end of the rack **6"**. The piston rod **32"** is generally elongate and is provided with a pressure foot **34"**. In use the pressure foot **34"** is disposed to abut the cartridge piston **14"**. The toothed gear **22"** is mounted on the end of the piston rod **32"** remote from the pressure foot **34"** in a journal bearing (not shown).

A dose dial sleeve **36"** of generally cylindrical form comprises a first section **38"** of first diameter and a second section **40"** of larger second diameter. The first section is located within the housing **2"**.

The second section **40"** of the dose dial sleeve **36"** is preferably of the same outer diameter as the housing **2"**. The second part **10"** of the housing **2"** comprises an external sleeve portion **42"** surrounding a coaxial internal sleeve portion **44"**. The external sleeve portion **42"** is closed to the internal sleeve portion **44"** at a circular internal flange portion **46"**. The first section **38"** of the dose dial sleeve **36"** is located within the second part **10"** of the housing **2"**, between the external sleeve portion **42"** and the internal sleeve portion **44"**. An inner surface of the first section **38"** and the outer surface of the internal sleeve portion **44"** are provided with interengaging features to provide a helical thread **48"** between the internal sleeve portion **44"** of the second part **10"** of the housing **2"** and the dose dial sleeve **36"**. This helical thread **48"** has the same lead as the internal thread of the drive sleeve **18"**, as noted above. Within the helical track, a helical rib provided on the inner surface of the dose dial sleeve **36"** may run. This enables the dose dial sleeve **36"** to rotate about and along the housing **2"**.

The second section **40"** of the dose dial sleeve **36"** is provided with an end wall **50"** adjacent its free end, which defines a central receiving area **52"** between the end wall **50"** and the free end of the dose dial sleeve **36"**. A through hole **54"** is provided in the end wall **50"**. A dose button **56"** of generally "T" shaped configuration is provided, the head **58"** of which is retained within the receiving area **52"** and the stem **60"** of which is sized to pass through the through hole **54"**. The stem **60"** of the button **56"** is provided with a plurality of fingers **62"**

that are deformable to pass through the through hole **54"** of the end wall **50"** only in the direction away from the free end of the dose dial sleeve **36"**.

The drive sleeve **18"** is closed at its end remote from the externally threaded section **24"** by an apertured end wall **64"** from which a plurality of engagement features **66"** project external to the drive sleeve **18"**.

A substantially U-shaped locking spring **68"** comprising first and second legs **70"**, **72"** joined by a link portion **74"** is provided for longitudinal mounting on the exterior of the drive sleeve **18"**. The link portion **74"** is of a length which is substantially equal to the external diameter of the drive sleeve **18"**. Each of the legs **70"**, **72"** of the locking spring **68"** terminates in a latch portion **76"**, the function of which will be described later.

When the device is assembled, the locking spring **68"** urges the dose button **56"** axially away from the piston rod **32"** and drive sleeve **18"**, towards the inside of the end wall **50"** of the dose dial sleeve **36"**. In this position, the dose button **56"** is locked with respect to rotation with the dose dial sleeve **36"**. The dose button **56"** is also permanently locked with respect to rotation with the drive sleeve **18"**.

An outer surface of the first section of the dose dial sleeve **36"** is provided with graphics **82"**. The graphics are typically a sequence of reference numerals. The housing **2"** is provided with an aperture or window **84"** through which a portion of the graphics, representing a dosage value selected by the user, may be viewed.

The graphics **82"** may be applied to the dose dial sleeve **36"** by any suitable means. The graphics **82"** may be printed directly on the dose dial sleeve **36"** or may be provided in the form of a printed label encircling the dose dial sleeve **36"**. Alternatively the graphics may take the form of a marked sleeve clipped to the dose dial sleeve **36"**. The graphics may be marked in any suitable manner, for example by laser marking.

The external circumferential flange **26"** which projects from the drive sleeve **18"** is provided with a pair of diametrically opposed through apertures **78"** sized to receive the corresponding latch portions **76"** of the locking spring **68"**. A clicker projection **80"** from the outer edge of the flange **26"** is associated with each through aperture **78"**.

In FIG. **18**, the drug delivery device is provided with a filled cartridge **4"**. To operate the drug delivery device a user must first select a dose. To set a dose the dose dial sleeve **36"** is rotated with respect to the housing **2"** until the desired dose value is visible through the window **84"**. The drive sleeve **18"** is linked to the dose dial sleeve **36"** and spirals out at the same rate during dialing. During the dialing of a dose, the locking spring **68** is straight and urges the dose button **56"** axially away from the piston rod **32"** and drive sleeve **18"**, towards the inside of the end wall **50"** of the dose dial sleeve **36"**, thereby providing a clutch mechanism. The drive sleeve **18"** therefore rotates over the toothed gear **22"** that is located inside it. The relative rotation between the drive sleeve **18"** and the housing **2"** causes an audible confirmation of the dose being dialed by engagement of the two clicker projections **80"** with the splines **30"** which extend along the internal surface of the first portion **8"** of the housing **2"**.

The limiting nut **28"** climbs up the drive sleeve **18"** in proportion to the dose dialed. The position of the limiting nut **28"**, which only moves along the external thread of the drive sleeve **18"** when there is relative rotation between the drive sleeve **18"** and the housing **2"**, corresponds to the amount of medicinal product remaining in the cartridge **4"**.

Once a desired dose has been set (as shown for example in FIG. **19**), to deliver the dose the user depresses the dose button **56"** to urge the button **56"** against the locking spring **68"**. As the dose button **56"** pushes down on the spring **68"**, the clutch between the dose button **56"** and the dose dial sleeve **36"** is disengaged. The axial force applied from the dose button **56"** onto the dose dial sleeve **36"** causes the dose dial sleeve **36"** to spin into the housing **2"** on the helical thread between the dose dial sleeve **36"** and the housing **2"**. The locking spring **68"** deforms and the legs of the spring move axially down the drive sleeve **18"**. The latch portions **76"** of the locking spring **68"** engage in the through apertures **78"** on the external flange **26"** which projects from the drive sleeve **18"** and maintain engagement between the clicker projections **80"** of the flange **26"** with the grooves between the splines **30"**, locking the drive sleeve to the housing **2"** and preventing the drive sleeve **18"** from rotation relative to the housing **2"** during dispensing of the dose. The drive sleeve **18"** is thus prevented from spinning and moves axially in, causing the toothed gear **22"** to rotate against the fixed rack **6"**. The toothed gear **22"**, together with the piston rod **32"** on which it is mounted, move along the rack **6"** a distance corresponding to one half of the distance by which the drive sleeve **18"** moves axially, creating a 2:1 mechanical advantage. This has the two-fold benefit of allowing the display on the dose dial sleeve **36"** to be larger for a given amount of travel of the piston **14"** within the cartridge **4"**, that is for a given amount of medicament to be dispensed and secondly of halving the force required to dispense the dose.

The piston rod **32"** is driven through the drive sleeve **18"** towards the first end of the drug delivery device, thereby to advance the cartridge piston **14"** and expel the desired dose of medicinal product. The piston rod **32"** continues to advance until the drive sleeve **18"** and dose dial sleeve **36"** have returned to their initial positions (FIG. **20**).

It can be seen that the dose selecting means and the dose expelling means extend beyond a second end of the housing **2"** as the dose is selected and are returned within the housing **2"** as the selected dose is expelled.

Further dosages may be delivered as required. FIG. **21** shows an example of a subsequently selected dosage. As noted above, the position of the limiting nut **28"** along the external thread of the drive sleeve **18"** corresponds to the amount of medicinal product remaining in the cartridge **4"**, such that when the nut **28"** reaches the external flange **26"** and can rotate no further this corresponds to no medicinal product remaining in the cartridge **4"**. It will be seen that if a user seeks to select a quantity of medical product greater than that remaining in the cartridge **4"**, this cannot be done since when the nut **28"** stops rotating against the drive sleeve **18"**, the drive sleeve **18"** and the housing **2"** will become locked together preventing rotation of the drive sleeve **18"** and hence the dose dial sleeve **36"**. This prevents the setting of a larger dose than the amount of medical product remaining within the cartridge **4"**. FIG. **22** shows a drug delivery device according to the present invention in which the entire medicinal product within the cartridge **4"** has been expelled.

The illustrated embodiment of the device according to the invention further comprises a maximum dosage dial end stop. When the dose dial sleeve **36"** is dialed fully out, the external flange **26"** on the drive sleeve **18"** engages the internal flange **46"** in the housing **2"**. It will be seen that if the user tries to dial beyond the maximum dosage, this cannot be done. When the drive sleeve **18"** stops rotating against the housing **2"**, the dose dial sleeve is also prevented from rotating. The reaction between the external flange **44"** and the internal flange **86"** indicates to the user that the maximum dose has been dialed.

The invention claimed is:

1. A drive mechanism for use in a drug delivery device comprising:

a housing having a helical thread;

a dose dial sleeve having a helical thread engaged with the helical thread of the housing;

a drive sleeve having two radially extending flanges spaced a distance apart and having an outer helical thread there between, where the drive sleeve is releasably connected to the dose dial sleeve;

a piston rod threadedly engaged with the drive sleeve; and

a clutch mechanism located between the dose dial sleeve and the drive sleeve.

2. A drive mechanism for use in a drug delivery device is provided comprising:

a housing having a helical thread along an inner surface,

a dose dial sleeve having a helical thread on an outer surface engaged with the helical thread of the housing;

a drive sleeve releasably connected to the dose dial sleeve; and

a clutch mechanism located between the dose dial sleeve and the drive sleeve;

wherein the clutch mechanism is configured such that,

a) when the dose dial sleeve and the drive sleeve are coupled, both are allowed to rotate with respect to the housing; and

b) when the dose dial sleeve and the drive sleeve are de-coupled, rotation of the dose dial sleeve with respect to the housing is allowed, while rotation of the drive sleeve with respect to the housing is prevented, whereby axial movement of the drive sleeve is allowed so that a force is transferred in a longitudinal direction to a proximal end of the drug delivery device.

3. The drive mechanism of claim 2 further comprising a piston rod having a first external thread and a second external thread, where the first external thread is threadedly engaged with an insert, and where the second external thread is threadedly engaged with an internal thread on the drive sleeve.

4. The drive mechanism of claim 2 where the drive sleeve has two radially extending flanges spaced a distance apart and having an outer helical thread there between and where the drive sleeve is releasably connected to the dose dial sleeve.

5. The drive mechanism of claim 4 further comprising a dose limiting mechanism.

6. The drive mechanism of claim 5 wherein said dose limiting mechanism is disposed between said first radially extending flange and said second radially extending flange.

7. The drive mechanism of claim 6 wherein said dose limiting mechanism comprises a nut threadedly engaged with the outer helical thread of the drive sleeve and is splined to an internal surface of the housing to prevent the nut from rotating while allowing relative longitudinal movement between the two radially extending flanges, whereby the longitudinal movement is proportional to dispensed doses.

8. A drive mechanism for use in a drug delivery device comprising:

a) a main housing having a first end and a second end, a helical thread having a first lead, an insert rotationally fixed to the housing having a thread with a second lead;

b) a dose dial sleeve having a helical thread engaged with the helical thread of the main housing configured so that during dose selection the dose dial sleeve rotates and extends axially from the second end of the main housing and during dose delivery rotates and moves axially back into the main housing;

c) a tubular drive sleeve having an internal surface and an outer surface having disposed thereon an intermediate thread, where the tubular drive sleeve is releasably connected to the dose dial sleeve through a clutch located between the dose dial sleeve and the tubular drive sleeve and where the tubular drive sleeve has an internal helical thread having a lead equal to the first lead;

d) a piston rod having a first external thread and a second external thread, where the first external thread has a lead equal to the second lead that is different and of opposite disposition than the first lead and is threadedly engaged with the insert, and where the second external thread is threadedly engaged with the internal thread of the tubular drive sleeve;

wherein,

when the dose dial sleeve and the tubular drive sleeve are coupled during dose section, both are allowed to rotate with respect to both the main housing and the piston rod; and

when the dose dial sleeve and the tubular drive sleeve are de-coupled during dose delivery, rotation of the dose dial sleeve with respect to the main housing is allowed, while rotation of the tubular drive sleeve with respect to the main housing is prevented, whereby axial movement of the tubular drive sleeve is allowed causing the piston rod to rotate through the tread of the insert and moving axially through the insert so that a force is transferred from the piston rod to a cartridge piston.

9. The drive mechanism of claim 8 wherein the intermediate thread is disposed between two radially extending flanges on the outer surface of the tubular drive sleeve.

10. The drive mechanism of claim 8 wherein the opposite disposition of the second lead of the first external thread compared to the first lead prevents the piston rod from moving during dose selection.

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,556,864 B2
APPLICATION NO.	: 13/075212
DATED	: October 15, 2013
INVENTOR(S)	: Robert Frederick Veasey et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page, item [30] Foreign Application Priority Data, please delete "0301822.0" and add --0304822.0--

Signed and Sealed this
Twenty-second Day of March, 2016

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office