IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

MYLAN PHARMACEUTICALS INC., MYLAN SPECIALTY L.P., and MYLAN INC., *Plaintiffs*, v. SANOFI-AVENTIS U.S. LLC, SANOFI S.A., AVENTIS PHARMA S.A., and SANOFI-AVENTIS PUERTO RICO INC. *Defendants*.	No. 2:23-cv-00836-MRH

MEMORANDUM IN SUPPORT OF
DEFENDANTS' MOTION TO DISMISS PLAINTIFFS' COMPLAINT

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INTRODUCTION

Mylan's complaint is a mishmash of unsupported theories and antitrust buzz words that fail to state a claim as a matter of law. Plaintiffs (collectively, "Mylan") allege that Sanofi-Aventis U.S. LLC and three of its corporate affiliates (collectively, "Sanofi") monopolized the market for "injectable insulin glargine" to protect their sales of Lantus® and Toujeo® and exclude Mylan's competing product, Semglee. One of Mylan's two primary theories—that Sanofi used "bundled" discounts to tie Lantus and Toujeo and exclude Semglee from the market—fails for at least four reasons. *First*, it fails as a matter of law because the complaint never alleges (as it must) that Sanofi bundled products across two different product markets. *Second*, Mylan tries to supplement its bundling theory with a conclusory allegation of an express exclusive dealing agreement, and a few nonsensical allegations of a "coercive product hop," all of which fail to plausibly support (let alone state) a claim. *Third*, Mylan fails to plead the required element of substantial foreclosure of the market. *Fourth*, Mylan fails to plausibly allege market power in a relevant market, which requires dismissal of the bundling theory and the entire monopolization claim.

Mylan's other theory is that Sanofi caused the Food and Drug Administration (FDA) to delay approval of Semglee by improperly listing patents in the agency's "Orange Book" and then asserting those patents in sham litigation against Mylan in order to trigger a statutory 30-month stay of FDA approval of Semglee. This theory has three foundational flaws. *First*, a claim concerning the 2013 patent listings and 2017 patent litigation is time-barred. *Second*, Mylan fails to plausibly allege that *Sanofi* caused FDA to delay Semglee's approval. Instead, Mylan's allegations, along with FDA's public records (of which the Court can take judicial notice), demonstrate that Mylan's *own* business decisions and failures—not the patent litigation—delayed FDA approval of Semglee. *Third*, independently, the sham litigation theory fails because Mylan does not plausibly allege that Sanofi's patent litigation was objectively baseless.

For all of these reasons, Mylan's claim under section 2 of the Sherman Act, along with its follow-on claims under federal and state law, must be dismissed for failure to state a claim under Federal Rule of Civil Procedure 12(b)(6). And even if Mylan had stated a claim against the hypothetical "Sanofi"—which the complaint defines as an amalgamation of the four defendants—the complaint fails to state a claim against each individually, because it does not attempt to plead that each defendant took actions giving rise to a claim for relief.

In addition, the complaint must be dismissed as to Sanofi S.A. for lack of personal jurisdiction under Federal Rule of Civil Procedure 12(b)(2). To carry its burden to establish personal jurisdiction, Mylan must allege that each defendant had requisite minimum contacts with the United States. But, other than to allege it is headquartered in France, the complaint lacks even a single allegation about the activities of Sanofi S.A., instead lumping the defendants together as "Sanofi," without even attempting to differentiate between them, or to allege (as Mylan must) that Sanofi S.A. took affirmative and specific steps to effectuate the alleged "scheme." This is facially deficient as a matter of law, and the complaint must be dismissed as to Sanofi S.A. for this reason as well.

LEGAL STANDARD

"To survive a motion to dismiss, a complaint must contain sufficient factual matter … to 'state a claim to relief that is plausible on its face.'" *Ashcroft v. Iqbal*, 556 U.S. 662, 678 (2009) (quoting *Bell Atlantic Corp. v. Twombly*, 550 U.S. 544, 570 (2007)). This requires factual allegations establishing all elements of a cause of action. *See Santiago v. Warminster Twp.*, 629 F.3d 121, 130 (3d Cir. 2010). "Threadbare recitals" of the elements, "conclusory statements" of fact, and mere "legal conclusions" "do not suffice" and are not accepted as true. *Iqbal*, 556 U.S. at 678. The allegations must "raise a right to relief above the speculative level," meaning that they must render the claim not merely "conceivable," but "plausible." *Twombly*, 550 U.S. at 555, 570.

ARGUMENT

I. MYLAN FAILS TO STATE A MONOPOLIZATION CLAIM UNDER THE SHERMAN ACT

Mylan's lead claim attempts—but fails miserably—to allege monopolization under section 2 of the Sherman Act. Compl. ¶ 234. To state a monopolization claim, a plaintiff must plausibly allege that the defendant possessed "monopoly power" in a relevant market and engaged in anticompetitive conduct. *Pac. Bell Tel. Co. v. linkLine Commc'ns, Inc.*, 555 U.S. 438, 447-48 (2009); *see Eisai, Inc. v. Sanofi Aventis U.S., LLC*, 821 F.3d 394, 402-03 (3d Cir. 2016) (discussing the element of "anticompetitive conduct"). A plaintiff must also allege "antitrust injury," which means injury to competition. *Brunswick Corp. v. Pueblo Bowl-O-Mat, Inc.*, 429 U.S. 477, 489 (1977). And a plaintiff must plead causation—a "causal connection between the purportedly unlawful conduct and the injury." *City of Pittsburgh v. West Penn Power Co.*, 147 F.3d 256, 265 (3d Cir. 1998). Mylan's section 2 claim must be dismissed in its entirety because each of its theories, considered separately or together, fails one or more of these required elements.

A. Mylan's Bundled-Discount Theory Fails To Allege Exclusionary Conduct Or Substantial Foreclosure Of A Market

Mylan's primary theory is that Sanofi excluded Semglee from the market by conditioning discounts for Lantus and Toujeo on "the inclusion of both" drugs on pharmaceutical formularies maintained by Pharmacy Benefit Managers (PBMs). Compl. ¶ 219; *see id.* ¶ 201 (heading L). According to Mylan, Sanofi used "bundling and conditional rebates" to coerce PBMs to purchase both Lantus and Toujeo, and not to purchase Semglee. *Id.* ¶ 208. Mylan invokes a litany of ominous terms to describe this theory: a "coercive market switch," a "coercive product hop," "bundling," "pairing," and "tying." *Id.* ¶¶ 3, 8, 13, 206, 208, 223. Shorn of empty labels, however, Mylan's theory boils down to allegations of exclusive dealing based on "bundled rebates." *LePage's Inc. v. 3M*, 324 F.3d 141, 154 (3d Cir. 2003) (en banc); *see also Cascade Health Sols. v.*

PeaceHealth, 515 F.3d 883, 894 (9th Cir. 2008) (analyzing "when bundled discounting can amount to anticompetitive conduct").

An exclusive dealing claim requires allegations of (1) some form of exclusive dealing arrangement, and (2) "substantial foreclosure" of the market, meaning the defendant entered into exclusive dealing arrangements with such a high proportion of buyers that it "severely restrict[ed] the market's ambit." *ZF Meritor, LLC v. Eaton Corp.*, 696 F.3d 254, 270-71 (3d Cir. 2012). Mylan comes nowhere close to plausibly alleging either element.

1. *The complaint fails to allege exclusionary conduct required for a bundling claim.*

"A bundled discount occurs when a firm sells a bundle of goods or services for a lower price than the seller charges for the goods or services purchased individually." *Cascade Health*, 515 F.3d at 894. "Bundled discounts generally benefit buyers because the discounts allow the buyer to get more for less." *Id.* at 895. In narrow circumstances, "bundled rebates and discounts" can "operate as exclusive dealing arrangements," *ZF Meritor*, 696 F.3d at 282, but this is "limited to cases in which a *single-product producer* is excluded through a bundled rebate program offered by a producer of multiple products, which conditions the rebates on purchases across *multiple different product lines*," *id.* at 274 n.11 (emphasis added); *see Eisai*, 821 F.3d at 405 (affirming this holding of *ZF Meritor*).

Bundling claims derive from "unlawful tying," which "cannot exist unless two separate product markets have been linked." *ZF Meritor*, 696 F.3d at 274 n.11 (quoting *Jefferson Parish Hosp. Dist. No. 2 v. Hyde*, 466 U.S. 2, 21 (1984)); *LePage's*, 324 F.3d at 155 (noting that bundling claims "are best compared with tying"). And competitive concerns about bundling arise only when the defendant's competitor "does not manufacture an equally diverse group of products and … therefore cannot make a comparable offer" for bundled discounts. *LePage's*, 324 F.3d at 155; *see*

Cascade Health, 515 F.3d at 897 ("[A] bundled discounter can exclude rivals who do not sell as great a number of product lines without pricing its products below its cost to produce them.").

Crucially, a different legal test for anticompetitive conduct—the "price-cost test" used for predatory pricing claims—applies when a plaintiff alleges discounts in a *single* product market. *ZF Meritor*, 696 F.3d at 274 n.11 ("Accordingly, we join our sister circuits in holding that the price-cost test applies to market-share or volume rebates offered by suppliers within a single-product market."). The price-cost test requires allegations that the defendant priced its goods below cost and had "a dangerous probability … of recouping its investment in below-cost prices" after its rival exited the market. *Id.* at 272.

a. ***Mylan fails to allege bundling across two separate product markets.*** Here, Mylan's complaint boils down to a theory of single-product rebates, which fails as a matter of law. Rather than alleging bundling of products in "separate product markets," *id.* at 274 n.11, the complaint takes great pains to allege that Lantus and Toujeo are the *same product* competing to fill the *same consumer demand*. Toujeo is, allegedly, "therapeutically indistinguishable" from Lantus, with "no unique therapeutic value." Compl. ¶¶ 3, 8, 22, 197, 202; *see also id.* ¶ 14 (no "patient benefit or medical necessity"). Customers allegedly are unwilling to pay more for Toujeo than Lantus because there is little additional benefit. *Id.* ¶¶ 12, 201. FDA itself allegedly found little difference between the drugs. *Id.* ¶ 196. And, according to Mylan, Sanofi believes that Toujeo and Lantus compete to fulfill the same demand and sought to "convert" Lantus users to Toujeo. *Id.* ¶¶ 12-14, 199-200.

Thus, in Mylan's own view of the world, Semglee competes directly with *both* Lantus and Toujeo, all in a single product market. According to Mylan, Lantus and Toujeo are perfect substitutes, and Semglee is biosimilar to (and since July 2021, interchangeable with) Lantus. *Id.*

¶¶ 15, 123, 138. Even the complaint's proposed market definition, "injectable insulin glargine," lumps all three products together by explicitly including "Lantus and Toujeo and their 'generic' or biosimilar equivalents." *Id.* ¶¶ 212, 215. Thus, the assertion that "Mylan did not, and does not, offer a competing product to Toujeo" (*id.* ¶ 210) is irreconcilable with Mylan's own description of the drugs and its alleged market definition, and cannot be credited. *See Dorley v. S. Fayette Twp. Sch. Dist.*, 129 F. Supp. 3d 220, 236 (W.D. Pa. 2015) ("[L]egal conclusions, or conclusory facts, may not contradict the detailed factual allegations of the Complaint."); *see also Bocker v. Hartzell Engine Techs., LLC*, 2023 WL 415792, at *4 & n.11 (D. Del. Jan. 26, 2023) ("Where a plaintiff's own pleading is internally inconsistent and contradictory, the court is not obligated to reconcile or accept such contradictory allegations.").

Because Semglee competes directly with both Lantus and Toujeo, Mylan *can* make a "comparable offer" for a discount without involving a second product market, unlike the plaintiff in *LePage's*, 324 F.3d at 155. There, LePage's could not compete with 3M's aggregate discount on tape and health care products because LePage's made only tape. *Id.* at 144-45. Here, Mylan can compete with Sanofi's aggregate discount on Lantus and Toujeo because Mylan's Semglee competes with both. If Sanofi offers an aggregate discount on 100 units of Lantus and 100 units Toujeo, Mylan can match the deal by offering the same discount on 200 units of Semglee. Thus, Mylan's allegation that "[i]t was economically impossible" for it to "cover this difference in a vacuum" (Compl. ¶ 17) is implausible, and fails the "common sense" test under *Iqbal*, 556 U.S. at 679.

Accordingly, Mylan's bundling claim fails as a matter of law because Mylan fails to allege bundling of products in "separate product markets." *ZF Meritor*, 696 F.3d at 274 n.11. Moreover, Mylan's failure to plead separate product markets means the price-cost test applies, *ZF Meritor*,

696 F.3d at 274 n.11, and Mylan does not even attempt to allege that Sanofi priced Lantus and Toujeo below cost. Quite the contrary, Mylan alleges that "Sanofi sold Lantus and Toujeo at prices well in excess of marginal costs," *see* Compl. ¶ 216.

Separately, Mylan alleges that Sanofi bundled rebates in contracts with State entities, such as Medicaid programs. *See* Compl. ¶¶ 15, 200, 226. That subset of Mylan's claims is barred by the *Noerr-Pennington* doctrine, under which a plaintiff cannot complain about "restraint[s] upon trade or monopolization" that are "the result of governmental action." *E. R.R. Presidents Conference v. Noerr Motor Freight, Inc.*, 365 U.S. 127, 136 (1961); *see Asphalt Paving Sys., Inc.*, *v. Asphalt Maint. Sols., LLC*, 2013 WL 1292200, at *4-7 (E.D. Pa. Mar. 28, 2013). Because Medicaid formularies are an outcome of governmental processes, *Noerr-Pennington* bars Mylan's claims based on discounts or rebates paid to those agencies. *See, e.g.*, *In re EpiPen Mktg., Sales Practices & Antitrust Litig.*, 336 F. Supp. 3d 1256, 1290-91 (D. Kan. 2018).

b. ***Mylan is not a single-product competitor.*** Mylan's bundling theory fails for the independent reason that it cannot plausibly allege it is a "single-product" competitor. *ZF Meritor*, 696 F.3d at 274 n.11. Because Mylan manufactures products other than Semglee, it can bundle Semglee discounts with discounts on those products to make a comparable offer to the discounts Sanofi offers for Lantus and Toujeo. *See Pfizer Inc. v. Johnson & Johnson*, 333 F. Supp. 3d 494, 503-04 (E.D. Pa. 2018) ("Pfizer, of course, is not a single-product producer. … J & J's multi-product bundles, on their own, therefore do not present antitrust concern."). While Mylan alleges it is a "single-product competitor," Compl. ¶ 13, this allegation fails to meet Rule 11 and need not be credited. For example, the complaint incorporates a Mylan press release explaining that Mylan manufactures "more than 1,100 generic pharmaceuticals and several brand medications." *See id.* ¶ 124 n.24. Further, FDA's Orange Book—a judicially noticeable public record (*see infra* p. 19)—

reveals that the Mylan plaintiffs had more than 300 drug products approved for sale in the United States in 2020, including at least 25 branded drugs.[1] This includes Mylan's popular "EpiPen" injector. *See In re EpiPen Mktg., Sales Practices & Antitrust Litig.*, 44 F.4th 959 (10th Cir. 2022).

Mylan's dozens of product lines are obviously as diverse (if not more so) than Sanofi's two-product Lantus-Toujeo bundle. Thus, if Mylan was for some reason unable to offer a competing discount bundle, it was required (and failed) to allege plausible facts in support of such a conclusion. *Pfizer*, 333 F. Supp. 3d at 504 ("Pfizer has not alleged any facts suggesting that J & J is hindering its ability to compete with J & J's multi-product bundles by offering their own multi-product bundles."); *Shire US, Inc. v. Allergan, Inc.*, 375 F. Supp. 3d 538, 557 (D.N.J. 2019) ("Plaintiff—a large pharmaceutical company—has also not asserted that it did not have other available products that it could offer … as part of a bundled rebate."). Between two multi-product competitors like Sanofi and Mylan, bundled rebates merely represent "vigorous price competition," and do not state an antitrust claim as a matter of law. *EpiPen*, 44 F.4th at 1000.

c. ***Mylan's other exclusionary conduct allegations are wholly conclusory.*** Mylan unsuccessfully attempts to bolster its bundling theory with two other conclusory allegations of exclusionary conduct. *First*, a single sentence in Mylan's complaint alleges that Sanofi "conditioned rebates for Toujeo on PBMs' agreement to *exclude* biosimilar insulin glargine products from formularies." Compl. ¶ 11 (emphasis added). But Mylan never pleads any facts in support of this allegation, such as alleging the existence of a specific exclusivity agreement, the PBM with whom any such agreement existed, when it was adopted, or how long it was in effect.

[1] FDA, *Approved Drug Products With Therapeutic Equivalence Evaluations* ("Orange Book"), Appendix B, at 120-27 (40th ed. 2020), https://wayback.archive-it.org/7993/20201222044046/https:/www.fda.gov/media/71474/download (**Exhibit A**) (highlighting in yellow the Mylan plaintiffs and in pink the branded drugs).

Furthermore, Mylan's repeated allegation that Sanofi conditioned its rebates on *inclusion* of Lantus and Toujeo on formularies does not save this solitary *exclusion* allegation, because Mylan never alleges that including Lantus and Toujeo on formularies meant excluding other products. *See, e.g.*, *id.* ¶ 219 ("conditioning rebates for either product on the inclusion of both on formularies"); *accord id.* ¶¶ 3, 10, 11, 17, 203, 204, 247; *see id.* ¶ 201 (heading L) ("Sanofi Conditioned Rebates for Lantus on the Inclusion of Toujeo").

Second, Mylan gets nowhere by sprinkling conclusory allegations of a "coercive product hop." Compl. ¶¶ 8, 223, 236, 252. The complaint does not try to allege a viable product-hopping claim, which would require (at minimum) an allegation that Sanofi "withdrew" Lantus "from the market," resulting in a "hard switch" to Toujeo. *New York ex rel. Schneiderman v. Actavis PLC*, 787 F.3d 638, 648, 655 (2d Cir. 2015); *see also Mylan Pharms. Inc. v. Warner Chilcott Pub. Ltd. Co.*, 838 F.3d 421, 429 (3d Cir. 2016) ("*Doryx*") (rejecting product-hopping claim, even where Mylan alleged that defendant "pulled older versions [of the drug] from the market"); *In re Asacol Antitrust Litig.*, 233 F. Supp. 3d 247, 269 (D. Mass. 2017) (collecting cases, and dismissing product-hopping claim because defendant "maintained both products on the market"). Here, the complaint alleges the opposite of a product hop: Sanofi allegedly used bundling to ensure Lantus *remained available*. *See* Compl. ¶ 3 ("the tying of rebates began to work in reverse, with Toujeo protecting Lantus"). Indeed, not only does Lantus remain on the market, but the complaint alleges that it was still far outselling Toujeo in 2020. Compl. ¶ 18.

2. *The complaint fails to plausibly allege market foreclosure.*

Mylan's bundling theory also must be dismissed for failing to plausibly allege "substantial foreclosure" of the market. *ZF Meritor*, 696 F.3d at 271. "To demonstrate substantial foreclosure, a plaintiff 'must both define the relevant market and prove the degree of foreclosure.'" *Eisai*, 821 F.3d at 403. The challenged practice must "bar a substantial number of rivals or severely restrict

the market's ambit." *Id.* Here, the complaint not only fails to plausibly allege a relevant market, as discussed below (p. 11), but it fails to allege any degree of foreclosure. For example, the complaint fails to allege basic facts about the market that would permit a plausible inference of market foreclosure, such as how many PBMs exist, whether there are other buyers besides PBMs, whether Sanofi entered into agreements with a large proportion of buyers, how many rivals exist, and whether Sanofi's alleged bundled discounts excluded a substantial portion of the market from those rivals.

Worse still, the complaint admits the presence of other market rivals that have *not* been foreclosed. Eli Lilly introduced a competing insulin glargine, Basaglar, in 2016. Compl. ¶¶ 194, 214. Novo Nordisk has long sold a basal insulin, Levemir. *Id.* ¶ 194. Despite knowing this, Mylan fails to allege whether and to what extent Sanofi's conduct affected *the market*, including other rivals. *Cf.* Phillip E. Areeda & Herbert Hovenkamp, *Antitrust Law: An Analysis of Antitrust Principles and Their Application*, ¶ 749d (4th ed. 2022) ("[W]e would not extend the [bundled-discount] doctrine to any situation in which there was at least one competing firm able to match the defendant's discount across all product lines."). The complaint similarly fails to allege whether Sanofi's conduct "restrict[ed] the market's ambit," that is, whether any buyers were "reasonably available" to competitors. *Eisai*, 821 F.3d at 403. By contrast, in *ZF Meritor*, the defendant entered into agreements with "every direct purchaser in the market." 696 F.3d at 287; *see also United States v. Dentsply Int'l, Inc.*, 399 F.3d 181, 196 (3d Cir. 2005) (defendant's "grip on its 23 authorized dealers effectively choked off the market"); *LePage's*, 324 F.3d at 160 (defendant cut off "key retail pipelines").

At bottom, the complaint fails to allege market foreclosure, and for this independent reason the bundling theory and any other exclusive dealing theory must be dismissed.

B. Mylan Fails To Plausibly Define A Relevant Market Or Allege Market Power

Mylan's entire monopolization claim must also be dismissed because the complaint fails to define a relevant market and fails to plausibly allege market power.

1. *The complaint ignores substitute products and therefore fails to define a relevant market.*

Mylan must define the relevant market for two independent reasons. First, claims of monopolization or attempted monopolization require, respectively, proof of market power or a dangerous probability of achieving market power. *Doryx*, 838 F.3d at 433. Direct evidence of market power is "rarely available." *Id.* at 434. More commonly, a plaintiff must rely on "indirect evidence," by showing that the defendant possesses a large share of the relevant market and that there are barriers to entry. *Id.* at 435. This method obviously "requires a definition of the relevant market." *Id.* Mylan contends it need not define the relevant market because it has direct evidence, Compl. ¶¶ 219-20, but its allegations are wholly conclusory, as explained below. And in any event, the complaint must certainly plead a relevant market to show *attempted* monopolization, because "direct measures of market power can, of course, detect only present power," whereas an attempted monopolist seeks to obtain power "that does not yet exist." Areeda & Hovenkamp ¶ 531d.

Second, and independently, the complaint must define the relevant market because, as explained above, Sanofi's alleged exclusive-dealing conduct is only anticompetitive if it resulted in substantial foreclosure of the market, which naturally requires defining the relevant market. *Eisai*, 821 F.3d at 403. Mylan thus cannot possibly escape its burden of plausibly alleging a relevant market. Failing that burden, the monopolization claim must be dismissed.

A relevant market must include all products that are reasonably interchangeable for the same use, based on price, use, qualities, and cross-elasticity of demand. *Queen City Pizza, Inc. v. Domino's Pizza, Inc.*, 124 F.3d 430, 437 (3d Cir. 1997). Products are interchangeable when "either

would work effectively," regardless of "some degree of preference for one product over the other." *Doryx*, 838 F.3d at 436 (cleaned up). If a complaint "alleges a proposed relevant market that clearly does not encompass all interchangeable substitute products," the market definition is "legally insufficient" and the complaint may be dismissed. *Queen City Pizza*, 124 F.3d at 436; *see also, e.g.*, *Re-Alco Indus., Inc. v. Nat'l Ctr. for Health Educ., Inc.*, 812 F. Supp. 387, 391-92 (S.D.N.Y. 1993) (requiring a complaint to "allege facts regarding substitute products" and to "distinguish among apparently comparable products" to avoid dismissal); *N. Penn Towns, LP v. Concert Golf Partners, LLC*, 554 F. Supp. 3d 665, 698-99 (E.D. Pa. 2021) (collecting cases failing to allege facts distinguishing products in proposed market from apparently related products).

Mylan alleges that the relevant market is limited to injectable insulin glargine. Compl. ¶ 220. But it acknowledges that there are "other insulin product[s]." *Id.* ¶ 214. Specifically, Mylan alleges that Lantus fits in the category of "basal" or "long-acting" insulins, *id.* ¶ 89, and repeatedly refers to the category of "basal" insulin, *id.* ¶¶ 8, 12, 14, 89, 195, 201, 208. Mylan alleges that Lantus was competing with basal insulins other than glargine. *Id.* ¶ 14 ("convert basal insulin, especially glargine users"). And the figure in paragraph 194 identifies some non-glargine basal insulins, such as Levemir and Tresiba, with which Lantus and Toujeo compete. The "Drug Pricing Report," which the complaint incorporates by reference, states explicitly that Levemir "competes with Sanofi's long-acting insulin product, Lantus."[2] The "Insulin Report Documents," which the complaint also incorporates by reference, suggests an even wider field of competition,

[2] U.S. Committee on Oversight and Reform, Majority Staff Report, *Drug Pricing Investigation* 26 (Dec. 2021) https://oversightdemocrats.house.gov/sites/democrats.oversight.house.gov/files/DRUG%20PRICING%20REPORT%20WITH%20APPENDIX%20v3.pdf.

showing that Lantus's "Competitor Products" also include premixed analog insulins, such as "Humalog Mix" and "Novolog Mix."[3]

Despite these obvious potential competitors, the complaint fails to include allegations differentiating insulin glargine from other insulins and fails to allege a relevant market as a result. *See*, *e.g.*, *URL Pharma, Inc. v. Reckitt Benckiser, Inc.*, 2015 WL 5042911, at *5 (E.D. Pa. Aug. 25, 2015) (alleging distinctions between guaifenesin and other drugs). Indeed, the complaint makes only the bare assertion that "injectable insulin glargine products do not exhibit significant, positive cross-elasticity of demand with respect to price with any other insulin product." Compl. ¶ 214. Under Rule 8, however, such "bare assertions" are "not … assumed true." *Iqbal*, 556 U.S. at 681. Because Mylan fails to plausibly allege a relevant market, its monopolization and attempted monopolization claims must be dismissed.

2. *The complaint fails to allege market power.*

Mylan also fails to plausibly allege market power using either direct or indirect evidence. This is yet another independent reason for dismissing the monopolization claim in its entirety.

No direct evidence of market power. Monopoly power means that a firm "can profitably raise prices without causing competing firms to expand output and drive down prices." *Doryx*, 838 F.3d at 434. A plaintiff must therefore show "both that the defendant had an 'abnormally high price-cost margin' and that the defendant 'restricted output.'" *Id.* at 434; *see URL Pharma*, 2015 WL 5042911, at *4-5 (rejecting direct-evidence approach where complaint failed to include "any factual pleadings pertaining to … **both** supracompetitive prices and restricted output"); *Geneva Pharms. Tech. Corp. Barr Labs. Inc.*, 386 F.3d 485, 500 (2d Cir. 2004) (requiring "analysis of

[3] U.S. Senate Finance Committee, *Documents Produced by Sanofi in Insulin Investigation* 79, 237 (2021), https://www.finance.senate.gov/imo/media/doc/Sanofi_Redacted.pdf.

[the defendant's] costs" indicating an "abnormally high price-cost margin" and "evidence that the defendant restricted output"). But direct evidence is "only 'rarely available.'" *Doryx*, 838 F.3d at 434. Given this rarity, specific factual allegations are critical, because "determining whether a complaint states a plausible claim is context specific," *Iqbal*, 556 U.S. at 663, and Rule 8 does not "unlock the doors of discovery for a plaintiff armed with nothing more than conclusions," *id.* at 678-79.

While Mylan purports to chart the rare route of alleging market power based on direct evidence (Compl. ¶¶ 216-17, 219, 222), its complaint does not include any assertions indicating that Mylan has data, or even that data exists, to demonstrate market power directly. First, it never alleges Sanofi restricted output, which is fatal. Second, Mylan *admits* that an allegation that Sanofi had abnormally high margins is based only on "information and belief." Compl. ¶ 216. This amounts to "nothing more than a 'formulaic recitation of the elements'" that is "not entitled to be assumed true." *Iqbal*, 556 U.S. at 681. Mylan's other purported allegations of direct evidence of market power, in paragraph 219, merely summarize Mylan's theories of liability and do not purport to plead that Sanofi restricted output or to provide facts indicating abnormal price-cost margins. Mylan's allegations of direct evidence of market power therefore fail.

No indirect evidence of market power. Monopoly power may also be inferred from indirect evidence, but "a plaintiff typically must plead and prove that a firm has a dominant share in a relevant market, and that significant 'entry barriers' protect that market." *Broadcom Corp. v. Qualcomm Inc.*, 501 F.3d 297, 307 (3d Cir. 2007). Determining whether the defendant has a dominant market share "requires a definition of the relevant market." *Id.* And a dominant share means "significantly larger than 55%." *Doryx*, 838 F.3d at 437. Barriers to entry are factors "that prevent new competition from entering a market in response to a monopolist's supracompetitive

prices," such as "regulatory requirements, high capital costs, or technological obstacles." *Broadcom*, 501 F.3d at 307.

As discussed above, the complaint fails to define the relevant market. But even if it did, Mylan does not allege any facts describing Sanofi's share of that market (whether that be insulin glargine, basal insulin, or insulin more broadly). While the complaint contains statistics about Lantus and Toujeo sales relative to *each other*, Compl. ¶¶ 18, 209, the complaint says nothing about their share of a relevant market.

The complaint also fails to plausibly allege high barriers to entry. Its single-sentence allegation that Sanofi "enjoyed high barriers to entry" is conclusory—it does not even identify a barrier, much less plead facts in support of that conclusion. *See* Compl. ¶ 218. Mylan must plead that new market entrants "will be unable" to enter the market for specific reasons. *SEI Glob. Servs., Inc. v. SS&C Advent*, 496 F. Supp. 3d 883, 895 (E.D. Pa. 2020). But the complaint, and the Drug Pricing Report it incorporates by reference, show that Novo Nordisk, Eli Lilly, and Mylan itself have developed competing insulin glargine products and other basal insulin products and have entered the market. The complaint's conclusory allegation that new entrants will face barriers is again nothing more than a "formulaic recitation" of one of the elements. *Iqbal*, 556 U.S. at 681.

Mylan also asserts an attempted monopolization claim (*see infra* p. 25), which requires pleading that the defendant has "a dangerous probability of achieving monopoly power." *Pastore v. Bell Tel. Co. of Pa.*, 24 F.3d 508, 512 (3d Cir. 1994). Evidence of such danger dovetails with evidence of present monopoly power. The "[m]ost significant" factor "is the defendants' share of the relevant market." *Id.* at 513. Other factors include "the strength of the competition, probable development of the industry, the barriers to entry, the nature of the anti-competitive conduct, and the elasticity of consumer demand." *Id.*

Once again, even if the complaint had plausibly defined a relevant market, the complaint fails to allege Sanofi's share of it. The complaint's allegations of barriers to entry and demand elasticity are conclusory, as explained above, and the complaint says nothing about the strength of other rivals or the probable development of the industry. *See Phila. Taxi Ass'n v. Uber Techs., Inc.*, 886 F.3d 332, 342 (3d Cir. 2018) ("[E]asy entry—particularly historical evidence of entry—is even more significant in the attempt case than in monopolization cases generally.").

C. Mylan's Claim That Sanofi's Conduct Delayed FDA Approval For Semglee Is Time-Barred And Fails For Lack Of Causation

Mylan's other theory—that Sanofi improperly listed invalid patents in FDA's Orange Book and asserted those patents in litigation in order to "delay[] regulatory approval" of Semglee (Compl. ¶ 3)—fares no better. The heart of this claim arises from the Hatch-Waxman Act, which provides a pathway for "streamlining the drug approval process," as well as "specialized procedures for brand-name and generic drug manufacturers to resolve intellectual property disputes" (including the 30-month stay of FDA's approval of Semglee at issue in this case). *See In re Wellbutrin XL Antitrust Litig. Indirect Purchaser Class*, 868 F.3d 132, 143-44 (3d Cir. 2017).

According to Mylan, Sanofi's Orange Book listings in 2013 somehow caused Mylan to delay seeking FDA approval of Semglee until 2017. Compl. ¶¶ 127-28. Once Mylan applied for FDA approval, Sanofi allegedly filed a sham lawsuit that triggered the statutory 30-month stay of approval of Mylan's application from October 2017 to March 2020. *See id.* ¶¶ 3, 4, 152, 157. According to Mylan, it suffered an antitrust injury because it was not able to launch Semglee "until late 2020, many years after it should have." *Id.* ¶¶ 191-93, 228. This theory fails, both because Mylan does not plausibly plead causation and because the claim is time-barred.

1. An antitrust plaintiff must establish "antitrust injury … caused by the antitrust violation—not a mere causal link, but a direct effect." *West Penn*, 147 F.3d at 268. Binding Third

Circuit precedent holds that to establish a claim for anticompetitive Hatch-Waxman litigation, a plaintiff must plead and prove that the litigation caused an injury to competition by preventing entry of a competing drug that "could have launched … in the absence of the 30-month stay." *Wellbutrin*, 868 F.3d at 151-52. Mylan fails to plausibly allege that Sanofi caused FDA to delay approval of Semglee, either by listing patents in the Orange Book in 2013 or by triggering the 30-month stay in 2017. Indeed, Mylan's own allegations, along with judicially noticeable facts from public records, flatly contradict the contention that the Orange Book listings or 30-month stay caused FDA to delay regulatory approval for Semglee or otherwise delayed Semglee's launch.

First, Mylan absurdly alleges that *Sanofi* is to blame because Mylan delayed filing its own drug application for Semglee from 2013 to 2017. Compl. ¶¶ 127-28. As the complaint explains, Mylan delayed its application because the Biologics Price Competition & Innovation Act ("BPCIA") "complicate[d] Mylan's path" to approval. *Id.* The BPCIA was enacted in 2010 and provided that regulation of certain biosimilar products approved as drugs under the Food, Drug & Cosmetic Act would transition to regulation under the Public Health Services Act ten years later, on March 23, 2020. *Id.* ¶ 56. Mylan contends that its failure to file until 2017 "would have been avoided" if not for two patents Sanofi listed in the Orange Book "by November 2013." Compl. ¶¶ 127-29. But Mylan's own allegations show that Mylan failed to file any sooner because it was engaged in a protracted dialogue with FDA about the type of application to file in light of the upcoming transition to the BPCIA. *Id.* Mylan admits that, "[a]s late as June 2016, Mylan was still inquiring of FDA whether a traditional ANDA approach, 505(b)(2), or different pathway would be appropriate for Mylan's application," Compl. ¶ 128, and that Mylan submitted its 505(b)(2) application for Semglee on April 27, 2017, "after finally receiving guidance from the FDA on the best regulatory path forward," Compl. ¶ 129. These allegations lay bare the fact that Sanofi's

patents had no logical bearing on *Mylan's* discussions with FDA or its decision about the type of drug application to file.[4] Rather, Mylan clearly had an incentive to delay filing in the hopes of convincing FDA to allow Mylan to follow the cheaper and faster ANDA route. It was this negotiation with FDA—not Sanofi's patents—that delayed Mylan's filing of its Semglee 505(b)(2) application until 2017.

Second, Mylan alleges that, once it got around to filing its drug application in 2017, the 30-month stay still acted as an impediment to Semglee's approval. Compl. ¶ 133. This is implausible for three distinct reasons.

a. To begin, Mylan does not allege, as it cannot, that FDA granted tentative approval for Semglee during the stay. Mylan acknowledges that tentative approval is the mechanism FDA uses to indicate that approval is warranted absent a stay: "The FDA may grant a 505(b)(2) application tentative approval when it determines that the application would otherwise be ready for final approval were it not for the regulatory 30-month stay. Tentative approval is granted only when the applicant satisfies all scientific and procedural preconditions to final approval." Compl. ¶ 78.[5] By its own admission, Mylan's application was not "ready for final approval" at any point during the 30-month stay. *See id.*

b. Nor can Mylan blame Sanofi for the alleged "regulatory dead zone" caused by the transition of insulin products to regulation under the BPCIA. Compl. ¶¶ 128 (heading H), 131-33. Rather, Mylan found itself in this position due to a statutory scheme and its *own delay* in filing its

[4] Mylan would have been subject to the same patent certification requirements under the Hatch-Waxman Act for any patents listed in the Orange Book and the same 30-month stay whether Mylan filed an ANDA or a 505(b)(2) application. See 21 U.S.C. §§ 355(b)(2)(A), 355(j)(2)(A)(vii).

[5] By contrast, FDA granted tentative approval to two other insulin glargine products during this time. *See* Tentative Approval Letter for Eli Lilly's Basaglar, NDA 205692 (Aug. 18, 2014), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/205692Orig1s000TAltr.pdf; Tentative Approval Letter for Merck's Lusduna, NDA 208722 (July 19, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/208722Orig1s000TAltr.pdf.

New Drug Application ("NDA")—a delay that had nothing to do with Sanofi's patents, which were in the Orange Book "by November 2013." Compl. ¶ 127. A 30-month stay does not start until after an NDA containing a paragraph IV certification is filed. Compl. ¶ 76. If Mylan had not waited so long to file its NDA, the 30-month stay would not have butted up against the BPCIA transition date in March 2020.

c. Worse yet for Mylan, publicly available FDA documents (of which the Court can take judicial notice) make clear what the complaint tries to obscure: any delay in FDA approval of Semglee was caused *not* by the 30-month stay, but by Mylan's numerous failures to comply with the overarching regulatory scheme for approving new drugs.[6] The Court may take judicial notice of these matters of public record, which are carefully omitted from the complaint despite Mylan's obvious awareness of and implicit reliance on such documents, as well as its explicit reliance on comparable FDA documents for Lantus and Toujeo. *See, e.g.*, *Pension Benefit Guar. Corp. v. White Consol. Indus., Inc.*, 998 F.2d 1192, 1196 (3d Cir. 1993); *Starks v. Coloplast Corp.*, 2014 WL 617130, at *1 & n.3, *2 (E.D. Pa. Feb. 18, 2014) ("FDA reports published on the FDA website are public records that the court may judicially notice."); *see also* Compl. ¶¶ 136 (quoting from FDA's "approval letter" for Semglee), 95 n.22 (citing FDA's supplemental approval for Lantus), 195 n.31 (citing FDA's summary review for Toujeo). Specifically, the FDA approval documents show that Mylan delayed its own filing for over three years until April 2017 for two different reasons: (1) it was attempting to persuade FDA to award a therapeutic equivalence designation for Semglee, which would have allowed pharmacists in many states to automatically substitute

[6] *See* FDA, *Drug Approval Package*: SEMGLEE, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210605Orig1s000TOC.cfm (last accessed September 14, 2023).

Semglee for Lantus (Compl. ¶ 81); and (2) Mylan was still conducting the studies necessary to support its application.[7]

And, after Mylan filed its NDA in April of 2017, FDA issued a "Refusal to File" decision on June 26, 2017, *because Mylan's initial application was "not sufficiently complete to permit a substantive review."*[8] As the letter explained, Mylan's application was deficient because it sought approval for an "insulin glargine product manufactured using Process VI at a facility in Malaysia (i.e., Process VI product), while the insulin glargine product studied in the Phase 3 clinical trials was manufactured using Process V at a different facility in India (i.e., Process V product)."[9] FDA deemed this a "major" "manufacturing change" that required Mylan to submit "additional clinical safety and efficacy bridging data."[10] Notwithstanding this defect—which had *nothing* to do with anything Sanofi did—Mylan requested that its application be "Filed over Protest" on August 31, 2017. Compl. ¶ 134. Over the next two years, FDA issued not one, but *two* "Complete Response Letters" stating that it "[could not] approve this application in its present form" due to "major deficiencies,"[11] including, among others, the absence of the necessary "bridging data," as well as persistent "objectionable conditions" at the Semglee manufacturing facility in Malaysia.[12] Indeed, these judicially noticeable FDA records show that FDA was still reviewing Mylan's December 16, 2019 Second Resubmission—which it filed solely to address a *second* failed inspection of the Semglee manufacturing facility—when the 30-month stay expired on March 18, 2020.

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[7] Memorandum of Meeting Minutes at 2-3, 8, 11 (Mar. 7, 2014) (**Exhibit B**), in FDA, Administrative and Correspondence Documents, IND 105279/NDA 210605, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210605Orig1s000AdminCorres.pdf (hereinafter "Administrative Correspondence").

[8] Refusal to File Letter at 1 (Jun. 26, 2017) (**Exhibit C**), in Administrative Correspondence.

[9] *Id.*

[10] *Id.*

[11] Complete Response Letter at 1 (May 17, 2018) (**Exhibit D**), and Complete Response Letter at 1 (Aug. 28, 2019) (**Exhibit E**), in FDA, Other Action Letters, NDA 210605, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210605Orig1s000OtherActionLtrs.pdf.

[12] Exhibit D at 1-2; Exhibit E at 1.

In sum, the 30-month stay had no bearing on the timing of FDA approval for Semglee. Mylan's conclusory and speculative allegations to the contrary, which conflict with other allegations in the complaint and FDA's public records, fail to move the causation needle from impossible to "conceivable," let alone to actionable. *Twombly*, 550 U.S. at 555, 570. Thus, Mylan's claims must be dismissed to the extent they are based on any allegations that Sanofi caused FDA to delay approval of Semglee. *See West Penn*, 147 F.3d at 268 (affirming dismissal of antitrust complaint because "the interposition of the regulatory scheme and actions of the parties … interferes with the chain of causation"); *Wellbutrin*, 868 F.3d at 152-53 (rejecting argument that patent lawsuit "delayed Abrika's entry into the market" because there is "no evidence that Abrika could have launched even in the absence of the 30-month stay"); *id.* at 166 (reiterating that "no antitrust standing exists when a plaintiff's grievance is caused by a regulatory scheme rather than by the defendant's actions.").

2. Even if Mylan had adequately pleaded causation, its Orange Book-related claim would be barred by the statute of limitations. Under both federal and state law, an antitrust claim must be brought within four years of accrual, and a claim "accrues … when a defendant commits an act that injures a plaintiff's business." *Zenith Radio Corp. v. Hazeltine Research, Inc.*, 401 U.S. 321, 338 (1971); *see* 15 U.S.C. § 15b; N.J. STAT. ANN. §§ 56:9-14. "[T]he statute of limitations runs from the commission of the act." *Zenith Radio*, 401 U.S. at 338. Here, Mylan filed its complaint on May 17, 2023, which means the alleged "act" that injured Mylan must have been committed *after* May 17, 2019, for the complaint to fall within the statute of limitations.

Mylan alleges two acts by Sanofi that supposedly caused FDA to delay approval of Semglee, both of which occurred well before May 17, 2019: (1) the allegedly improper listing of patents in the Orange Book "by November 2013" (Compl. ¶¶ 127-28); and (2) the allegedly sham

patent infringement litigation filed on October 24, 2017. Compl. ¶¶ 145-46, 152. As to the latter, it makes no difference that the lawsuit progressed after October 2017, or that the stay was in effect for 30 months. "[T]he limitation period for monopolization by a wrongfully filed lawsuit runs from either the date the suit is filed or the date that the suit's defendant receives the process." Areeda & Hovenkamp ¶ 320; *P & M Servs., Inc. v. Gubb*, 2008 WL 4185903, at *5 (E.D. Mich. Sept. 8, 2008) ("[T]he operative overt act for purposes of the antitrust limitations statute is the filing of the sham lawsuit"), *aff'd*, 372 F. App'x 613 (6th Cir. 2010). As the Fifth and Ninth Circuits have explained, any "injury … resulting from continued prosecution" of the lawsuit "relates back to the initial decision to file." *Al George, Inc. v. Envirotech Corp.*, 939 F.2d 1271, 1274 (5th Cir. 1991) (quoting *Pace Indus. v. Three Phoenix Co.*, 813 F.2d 234, 238-39 (9th Cir. 1987)). Accordingly, whenever the supposed delay occurred, the claim for sham litigation accrued in October 2017 and is time-barred.[13]

D. Mylan's Sham Litigation Allegations Fail *Twombly*

Separately, the allegations of sham litigation must be dismissed because the complaint fails to allege facts that would overcome the First Amendment protection afforded to Sanofi's patent

[13] An unpublished decision of the Third Circuit also supports this argument. In *Perrigo Co. v. AbbVie Inc.*, the plaintiff asserted a monopolization claim based on sham litigation triggering a 30-month FDA stay. 2022 WL 2870152, at *4 (3d Cir. July 21, 2022). The court held that claim accrued "as soon as Defendants filed the Litigation." *Id.* at *4; *see id.* at n.10 ("The filing of a baseless lawsuit triggers the statute of limitations for antitrust claims based on that lawsuit."). As such, Mylan's alleged claim necessarily accrued on October 24, 2017, and is time-barred. Some language in the opinion, however, goes further and suggests that the triggering of a 30-month stay "necessarily delay[s] FDA approval." *Id.* at *4. But *Perrigo*'s reasoning in this regard conflicts with the published holding of the Third Circuit in *Wellbutrin*, 868 F.3d at 152-53. In *Wellbutrin*, the Third Circuit ruled that to prevail on a sham litigation claim a plaintiff must prove that the litigation caused antitrust injury by delaying a competing drug that "could have launched … in the absence of the 30-month stay." Further, the Court held that the 30-month stay in that case did not delay the competing drug because "FDA could not have approved" it absent the 30-month stay due to other regulatory bars. *Id.* at 151-53. In light of these authorities it is clear that (1) the limitations period begins to run when a sham lawsuit triggers the 30-month stay, *Perrigo*, 2022 WL 2870152, at *4 n.10; (2) any injury from delayed drug approval "relates back to the initial decision to file" the lawsuit, *Al George*, 939 F.2d at 1274; and (3) in all cases, a plaintiff must prove causation by showing that a competing drug "could have launched … in the absence of the 30-month stay," *Wellbutrin*, 868 F.3d at 151-52.

litigation under the Supreme Court's *Noerr-Pennington* doctrine. To overcome that immunity, a plaintiff must establish that the lawsuit was both "objectively baseless"—meaning the litigant had no "probable cause to initiate a suit"—and subjectively motivated by anticompetitive intent. *Wellbutrin*, 868 F.3d at 147. A plaintiff faces an especially "high[]" burden when alleging that patent litigation involving FDA approved drugs was "objectively baseless." *Id.* at 144, 149-51. Under the Hatch-Waxman Act, a drug applicant's "paragraph IV certification" that any relevant patents are invalid or not infringed "automatically counts as patent infringement." *Id.* at 144 (citing 21 U.S.C. § 355(j)(2)(A)(vii)); *see also* Compl. ¶¶ 70, 74, 76 (explaining paragraph IV certifications). Thus, a patent infringement suit under the Hatch-Waxman Act "could only be objectively baseless if no reasonable person could disagree with the assertions of noninfringement or invalidity in the certification." *Wellbutrin*, 868 F.3d at 149.

Mylan's allegations do not remotely approach (never mind meet) this standard. Mylan alleges that it sent a letter "notifying Sanofi it had filed … paragraph IV certifications and explaining its positions." Compl. ¶ 144. But the complaint fails to disclose the contents of Mylan's certification, and Mylan does not even attempt to allege that "no reasonable person could disagree" with its paragraph IV "assertions of noninfringement or invalidity." *Wellbutrin*, 868 F.3d at 149. Mylan's boilerplate allegations are insufficient to state a claim as a matter of law. *E.g.*, *Takeda Pharm. Co. v. Zydus Pharms. (USA) Inc.*, 2021 WL 3144897, at *12 (D.N.J. July 26, 2021) ("A boilerplate noninfringement assertion in an ANDA is insufficient to demonstrate objective baselessness"), *aff'd*, 2022 WL 17546949 (3d Cir. Dec. 9, 2022).

Mylan also asserts that the patents were *later* determined to be invalid by the Patent Trial and Appeal Board. Compl. ¶¶ 152-87. But an allegation that patents were *later* invalidated does *not* mean that asserting them in litigation was objectively bas eless from the start. *See Prof'l Real*

Est. Inv'rs, Inc. v. Columbia Pictures Indus., Inc., 508 U.S. 49, 60 n.5 (1993) ("[A] court must resist the understandable temptation to engage in *post hoc* reasoning by concluding that an ultimately unsuccessful action must have been unreasonable." (cleaned up)). The U.S. PTO examined the patent claims and issued every one of Sanofi's applications, after "thorough examination." *See* 37 C.F.R. § 1.104(a)(1); *Hyatt v. U.S. PTO*, 110 F. Supp. 3d 644, 646 (E.D. Va. 2015) (describing the "iterative process" of the patent examiner's "thorough examination"). Once issued, patents are "presumed valid" by statute (35 U.S.C. § 282(a)), and a patentee has an objective basis to presume the patent is valid *unless and until* it is later adjudicated invalid by a court or the PTO. *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 643 (2015) ("That presumption takes away any need for a plaintiff to prove his patent is valid to bring a claim."). Further, Mylan's allegations must be evaluated in light of the judicial record concerning those patents, which includes a strong dissent from one of the Federal Circuit judges serving on the panel reviewing the PTAB's invalidation of two of the patents. *See Sanofi-Aventis Deutschland GMBH v. Mylan Pharms. Inc.*, 791 F. App'x 916, 929-32 (Fed. Cir. 2019) (Newman, J., dissenting). It is not plausible to allege that it was objectively baseless for Sanofi to assert its patents in litigation when they were issued by the PTO, presumed valid by statute, and when at least one Federal Circuit judge deemed them valid. What's left is only the allegation that Sanofi had no "reasonable expectation of winning," Compl. ¶¶ 140, 146, a conclusory allegation that cannot survive *Twombly*. Mylan has failed to state a sham litigation claim.

* * *

Mylan's two theories of monopolization—using bundled discounts and delaying FDA approval of Semglee—fail for all the reasons stated above. This is true whether these theories are considered independently or as components of what Mylan calls a "multifaceted monopolization

scheme." Compl. ¶¶ 3, 236. As the Supreme Court has explained, a plaintiff cannot allege one claim "that cannot succeed with a [second] claim that cannot succeed, and alchemize them into a new form of antitrust liability." *linkLine*, 555 U.S. at 457. "Two wrong claims do not make one that is right." *Id.* Mylan's monopolization claim must be dismissed entirely.

II. MYLAN'S BACKUP CLAIMS MUST BE DISMISSED AS WELL

A. Mylan Fails To State A Claim For Attempted Monopolization, Exclusive Dealing Under Clayton Act Section 3, Or Violation Of New Jersey Antitrust Law

For all the same reasons discussed above, Mylan fails to state a claim in Counts II-IV. For an attempted monopolization claim under section 2 of the Sherman Act, a plaintiff must show "that the defendant (1) had specific intent to monopolize the relevant market, (2) engaged in anti-competitive or exclusionary conduct, and (3) possessed sufficient market power to come dangerously close to success." *Barr Labs., Inc. v. Abbott Labs.*, 978 F.2d 98, 112 (3d Cir. 1992). The plaintiff must also plead antitrust injury and causation. *West Penn*, 147 F.3d at 265. As explained above (*supra* pp. 16-24), the complaint fails to plead causation of any delay in FDA approval of Semglee, and fails to plead the sham litigation theory. It also fails to plead exclusive dealing through bundled discounts and substantial market foreclosure. *Supra* pp. 3-9. Finally, it fails to plead a dangerous probability of market power in a relevant market, which requires dismissal of the entire claim. *Supra* pp. 10-15. Of course, lacking any of these well-pleaded allegations, the complaint also fails to plausibly allege a specific intent to monopolize; Mylan's conclusory allegations of specific intent are insufficient.

For the exclusive dealing claim under section 3 of the Clayton Act, "the applicable law is the same" as under section 2 of the Sherman Act. *Eisai*, 821 F.3d at 402 & n.11. For the reasons stated above (*supra* pp. 3-9), the complaint fails to plead any form of exclusive dealing conduct, and fails to plead substantial market foreclosure.

And for the New Jersey state claim, New Jersey courts "follow federal antitrust law in interpreting [New Jersey's] antitrust statute." *Sickles v. Cabot Corp.*, 877 A.2d 267, 270-71 (N.J. Super. Ct. App. Div. 2005). Accordingly, the state claim must be dismissed for the same reasons given above.

B. Mylan Fails To State A Claim For Tortious Inducement Of Refusal To Deal

The complaint also fails to state a claim "for common law liability for tortious inducement of refusal to deal." Compl. ¶ 257. The complaint does not even allege which state law Sanofi supposedly violated, much less plead the elements of a claim under that unspecified source of state law. Assuming for the sake of argument only that Pennsylvania law applies, the complaint fails to allege any specific prospective contractual relationships—the first element of a claim for interference with prospective contractual relations. *See, e.g.*, *Salsgiver Commc'ns, Inc. v. Consol. Commc'ns Holdings, Inc.*, 150 A.3d 957, 964 (Pa. Super. Ct. 2016). A prospective contractual relationship is "something less than a contractual right, something more than a mere hope." *Thompson Coal Co. v. Pike Coal Co.*, 412 A.2d 466, 471 (Pa. 1979). It requires a "reasonable likelihood or probability" that a contract would have arisen absent the alleged interference. *Id.* (quoting *Glenn v. Point Park Coll.*, 272 A.2d 895, 898-99 (Pa. 1971)).

Here, the complaint merely states that "Mylan had a reasonable expectation of economic benefit from prospective contractual and economic relationships with thousands of purchasers, pharmacies, and diabetic patients across the country, all of whom would purchase Mylan's Semglee." Compl. ¶ 258. Nowhere, however, does Mylan identify these "thousands" of purchasers by name or with any degree of particularity. *See Alvord-Polk, Inc. v. F. Schumacher & Co.*, 37 F.3d 996, 1015 (3d Cir. 1994) (affirming summary judgment on tortious interference claim where plaintiffs "failed to identify with sufficient precision contracts and prospective contracts which were interfered with by the defendants"). Nor does Mylan plead any facts

supporting its conclusion that "all" of the unidentified purchasers would have purchased Semglee had they not been "induced into not dealing with Mylan" by Sanofi. *Id.* ¶ 260. Such vague and conclusory allegations fail *Twombly*, 550 U.S. at 555. Moreover, they reflect nothing more than Mylan's "mere hope" of prospective contractual relationships, as opposed to the "reasonable likelihood or probability" required to state a claim. *Thompson*, 412 A.2d at 471; *see also McLaughlin v. Int'l Bhd. of Teamsters*, *Local 249*, 641 F. Supp. 3d 177, 223 (W.D. Pa. Sept. 6, 2022) (dismissing tortious inducement claim based on plaintiff's "fail[ure] to set forth sufficient facts to establish a prospective employment relationship").

III. THE COMPLAINT IS AN IMPERMISSIBLE SHOTGUN PLEADING

The complaint is an impermissible shotgun pleading that fails to comply with Rule 8(a)(2). A shotgun pleading, among other things, "asserts multiple claims against multiple defendants without specifying which of the defendants are responsible for which acts or omissions." *Bartol v. Barrowclough*, 251 F. Supp. 3d 855, 859 (E.D. Pa. 2017) (cleaned up); *see also Hynson v. City of Chester, Legal Dep't*, 864 F.2d 1026, 1031 n.13 (3d Cir. 1988) (criticizing "shotgun pleading"). This fails "to give the defendants adequate notice of the claims against them and the grounds upon which each claim rests." *Bartol*, 251 F. Supp. 3d at 859; *see also Caristo v. Blairsville-Saltsburg Sch. Dist.*, 370 F. Supp. 3d 554, 569 n.21 (W.D. Pa. 2019) (Hornak, J.) ("Plaintiff must plead facts demonstrating the specific personal involvement of each Individual Defendant.") (collecting cases).

The opening paragraph of the complaint contains an unabashed mashup of three distinct Plaintiffs and four distinct Defendants: "Plaintiffs Mylan Pharmaceuticals Inc., Mylan Specialty L.P., and Mylan Inc. (collectively 'Mylan') bring this Complaint against Sanofi S.A., Sanofi-

Aventis U.S. LLC, Aventis Pharma S.A.,[14] and Sanofi-Aventis Puerto Rico Inc. (collectively 'Sanofi')." Compl. Intro. Thereafter, over 265 paragraphs and 5 counts, the complaint refers generally to "Mylan" and "Sanofi" without ever distinguishing which entity or entities allegedly did what and to which other entity or entities. By "[l]umping" the parties together, the complaint "fails to put Defendants on notice of their own alleged wrongdoing." *Campbell v. City of New Brunswick*, 2018 WL 2234899, at *3 (D.N.J. May 16, 2018); *see also Grande v. Starbucks Corp.*, 2019 WL 1455445, at *3 (E.D. Pa. Apr. 2, 2019) ("The defendants cannot defend the claims against them if they do not know which acts they allegedly committed and where those acts allegedly occurred.").

The complaint's melding of the various defendants also obscures the factual allegations necessary for the Court to determine whether Mylan has alleged plausible claims against each defendant as necessary under Rule 8. *See Ezekwo v. Jacobs*, 2023 WL 3848332, at *2 (D.N.J. June 6, 2023) (appeal pending) ("Such group pleading is also inappropriate and grounds for dismissal … because 'when defendants are grouped together, a court cannot determine whether a complaint has set forth plausible allegations as to each particular defendant.'"); *Mensah v. Manning*, 2020 WL 91089, at *6 (D.N.J. Jan. 8, 2020) ("[T]he Amended Complaint provides no other factual allegations of any acts specifically undertaken by any Defendant that would connect them to Plaintiff's alleged injuries, much less that would give rise to a plausible claim for relief.").

Here, Mylan alleges that the four Defendants, collectively defined, committed antitrust violations by improperly listing patents and litigating infringement claims, and by bundling rebates

[14] The complaint incorrectly identifies this defendant as "Aventis Pharma S.A." In December 2020, the form and name of the company changed under French law from a société anonyme ("S.A.") to a société à responsabilité limitée ("S.A.R.L."). Similarly, the complaint incorrectly uses the name "Sanofi S.A." While that entity is organized under French law as a société anonyme, the corporate designation "S.A." is not part of the entity's name. Nonetheless, for the avoidance of confusion, we refer to the two French defendants by the names used for them in the complaint: Sanofi S.A. and Aventis Pharma S.A.

for Toujeo and Lantus, but the complaint provides *no* indication whether or how each individual defendant participated in the alleged patent abuse or alleged monopolization. Indeed, the only fact individually alleged about Sanofi S.A. or Aventis Pharma S.A. is that each company conducts business *in France*. *See* Compl. ¶ 27 (alleging that Sanofi S.A.'s "principal place of business" is in "France"), ¶ 29 (same as to Aventis Pharma S.A.). The complaint is devoid of any factual allegations regarding how these entities, headquartered in France, participated in the alleged antitrust violations in the United States. The complaint does not even attempt to provide a plausible basis for Plaintiffs' claims against them.

Because Mylan's shotgun complaint fails to give the defendants notice as to conduct alleged against each, and because it falls short of the requirements of Rule 8 as to each defendant, the complaint should be dismissed in full. *See, e.g.*, *Grande*, 2019 WL 1455445, at *2-3; *Campbell*, 2018 WL 2234899, at *3; *Bartol*, 251 F. Supp. 3d at 859-61.

IV. MYLAN FAILS TO ALLEGE PERSONAL JURISDICTION OVER SANOFI S.A.

Relatedly, because it is a group pleading lacking any specific allegations as to any defendant, the complaint fails to plausibly allege that this Court has personal jurisdiction over French defendant Sanofi S.A. That defendant therefore moves to dismiss for lack of personal jurisdiction under Federal Rule of Civil Procedure 12(b)(2).

Consistent with due process, a court lacks personal jurisdiction over a defendant unless that defendant has sufficient "minimum contacts" with the forum. *D'Jamoos ex rel. Estate of Weingeroff v. Pilatus Aircraft Ltd.*, 566 F.3d 94, 102 (3d Cir. 2009). The relevant forum for purposes of this litigation is "the United States as a whole." *In re Auto. Refinishing Paint Antitrust Litig.*, 358 F.3d 288, 298 (3d Cir. 2004) (explaining the statutory basis for holding that "personal jurisdiction in federal antitrust litigation is assessed on the basis of a defendant's aggregate contacts with the United States as a whole.").

To evaluate minimum contacts, "[e]ach defendant's contacts with the forum … must be assessed individually." *Nicholas v. Saul Stone & Co. LLC*, 224 F.3d 179, 184 (3d Cir. 2000); *see Bristol-Myers Squibb Co. v. Super. Ct. of Cal., S.F. Cty.*, 582 U.S. 255, 268 (2017) (minimum contacts "must be met as to each defendant"). Further, jurisdiction over a local subsidiary does not establish jurisdiction over a foreign parent "because of the presumption of corporate separateness." *In re Enter. Rent-A-Car Wage & Hour Emp't Practices Litig.*, 735 F. Supp. 2d 277, 317 (W.D. Pa. 2010); *Daimler AG v. Bauman*, 571 U.S. 117, 134-35 (2014) (describing rule that "a subsidiary's jurisdictional contacts can be imputed to its parent only when the former is so dominated by the latter as to be its alter ego.").

"Once a defendant challenges a court's exercise of personal jurisdiction over it, the plaintiff bears the burden" to "'establish a prima facie case of personal jurisdiction.'" *D'Jamoos*, 566 F.3d at 102. Establishing a prima facie case requires that the plaintiff allege "the nature and extent" of each defendant's contacts with the forum "with reasonable particularity." *Gehling v. St. George's Sch. of Med., Ltd.*, 773 F.2d 539, 542 (3d Cir. 1985).

A plaintiff cannot satisfy this burden by lumping multiple defendants together into an undifferentiated mass, a tactic making it impossible to discern each defendant's alleged contacts with the forum. Courts have repeatedly dismissed complaints on that basis. In *Heartrepreneur, LLC v. Jones*, for example, the plaintiff alleged that six out-of-state defendants targeted in-state consumers, but the complaint "refer[ed] to all Defendants collectively and [did] not separately allege how each Defendant purposefully directed activities towards Pennsylvania." 2020 WL 2839102, at *3 (E.D. Pa. June 1, 2020). The court rejected that approach as insufficient under Supreme Court precedent: "Plaintiffs may not simply lump Defendants together to establish jurisdiction." *Id.* (citing *Calder v. Jones*, 465 U.S. 783, 790 (1984)). Similarly, in *Truinject Corp.*

v. Nestlé Skin Health. S.A., the plaintiff "attempt[ed] to create the impression that Nestlé Skin Health, S.A.'s role was significant by collectively defining all of the Corporate Defendants as 'Nestlé Skin Health' in the Complaint." 2020 WL 1270916, at *3 (D. Del. Mar. 17, 2020). The court rejected that approach, explaining that the collective definition made it "extremely difficult … to discern from the Amended Complaint which Defendant performed the alleged acts." *Id.* The court therefore granted the motion to dismiss: "Truinject's group pleading has resulted in a complaint that fails to meet its burden to allege sufficient facts to establish that this Court may properly exercise personal jurisdiction over Nestlé Skin Health, S.A." *Id.*; *see also Epstein v. Goodman Mfg. Co., LP*, 2015 WL 502033, at *4 (D.N.J. Feb. 4, 2015) ("[N]owhere in its brief does Elica specifically argue that SKF–Italy is subject to this Court's jurisdiction standing alone."); *id.* at *5 ("[T]o accept Elica's argument would be tantamount to disregarding the corporate form of over 80 entities.").

Here, the complaint's allegations regarding personal jurisdiction fall far short of being reasonably particular as to each defendant. The complaint's only individualized allegations as to Sanofi S.A. is that it is incorporated and headquartered *in France*, not the United States. Compl. ¶ 27. Thus, the complaint clearly fails to allege that Sanofi S.A. is "at home" in the United States for purposes of general personal jurisdiction. *See Daimler*, 571 U.S. at 138-39 (rejecting general personal jurisdiction because "neither Daimler nor MBUSA is incorporated in California, nor does either entity have its principal place of business there.").

Nor does the complaint make a prima facie case of specific personal jurisdiction over Sanofi S.A. based on contacts "[giving] rise to the liabilities sued on." *Id.* at 126. The remainder of the complaint's personal jurisdiction allegations do not distinguish among the defendants, instead alleging that the court has personal jurisdiction over "Sanofi," defined as all four

defendants. Compl. ¶¶ 31, 33-36. In support, the complaint alleges that "Sanofi"—again undifferentiated—manufactured, sold, and shipped Lantus and Toujeo in interstate commerce. *Id.* ¶ 34. The complaint also alleges, with no individual specificity, that "Sanofi" transacts business in the United States and that its actions were "directed at" the United States. *Id.* ¶¶ 35-36. The rest of the complaint's allegations use the same collective definition.

None of these paragraphs contain any factual allegations regarding Sanofi S.A.'s contacts with the United States. The use of the undifferentiated term "Sanofi" is blatantly inadequate to plead minimum contacts as to each defendant. Mylan may not "simply lump Defendants together to establish jurisdiction," *Heartrepreneur*, 2020 WL 2839102, at *3, because each defendant's contacts "must be assessed individually," *Nicholas*, 224 F.3d at 184. The complaint offers no plausible basis to conclude that Sanofi S.A.—a holding company that neither manufactures, markets, nor sells products—conducts any business whatsoever in the United States. Nothing else in the complaint identifies any activities that this defendant undertook anywhere, let alone in the United States. The complaint must therefore be dismissed as to Sanofi S.A. for lack of personal jurisdiction under Federal Rule of Civil Procedure 12(b)(2).

CONCLUSION

For the foregoing reasons, the Court should dismiss the complaint.

Dated: September 15, 2023

Respectfully submitted,

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IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF PENNSYLVANIA

MYLAN PHARMACEUTICALS INC., MYLAN SPECIALTY L.P., and MYLAN INC., *Plaintiffs*, v. SANOFI-AVENTIS U.S. LLC; SANOFI S.A.; AVENTIS PHARMA S.A., and SANOFI-AVENTIS PUERTO RICO INC., *Defendants*.	No. 2:23-cv-00836-MRH

DECLARATION OF AARON HEALEY IN SUPPORT OF DEFENDANTS' MOTION TO DISMISS PLAINTIFFS' COMPLAINT

I, Aaron Healey, make this declaration in support of Defendants Sanofi-Aventis U.S. LLC, Sanofi-Aventis Puerto Rico Inc., Sanofi S.A., and Aventis Pharma S.A.'s Motion to Dismiss Plaintiffs' Complaint.

1. I am a partner of the law firm Jones Day.

2. My business address is 250 Vesey Street, New York, NY, 10281.

3. I am a member in good standing of the bars of New York, Ohio, and Pennsylvania. My bar identification numbers are NY 4690400, OH 91709, and PA 310803.

4. I am admitted to practice in the United States District Court for the Western District of Pennsylvania.

5. I am counsel of record for Defendants Sanofi-Aventis U.S. LLC, Sanofi-Aventis Puerto Rico Inc., Sanofi S.A., and Aventis Pharma S.A.[1] in this matter.

[1] The Complaint incorrectly identifies this defendant as "Aventis Pharma S.A." In December 2020, the form and name of the company changed under French law from a société anonyme ("S.A.") to a société à responsabilité limitée ("S.A.R.L."). Similarly, the Complaint incorrectly uses the name "Sanofi S.A." While that entity is organized under French law as a société anonyme, the corporate designation "S.A." is not part of the entity's name. Nonetheless,

6. I certify that attached hereto are true and correct copies or excerpts of the following documents:

Exhibit	Document Description and Source
A	Excerpt from FDA, Approved Drug Products With Therapeutic Equivalence Evaluations ("Orange Book"), Appendix B (40th ed. 2020), https://wayback.archive-it.org/7993/20201222044046/https:/www.fda.gov/media/71474/download.[2]
B	Memorandum of Meeting Minutes (Mar. 7, 2014), in FDA, Administrative and Correspondence Documents, IND 105279/NDA 210605, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210605Orig1s000AdminCorres.pdf.
C	Refusal to File Letter (June 26, 2017), in FDA, Administrative and Correspondence Documents, IND 105279/NDA 210605, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210605Orig1s000AdminCorres.pdf.
D	Complete Response Letter (May 17, 2018), in FDA, Other Action Letters, NDA 210605, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210605Orig1s000OtherActionLtrs.pdf.
E	Complete Response Letter (Aug. 28, 2019), in FDA, Other Action Letters, NDA 210605, https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/210605Orig1s000OtherActionLtrs.pdf.

7. The attached documents are matters of public record "from sources whose accuracy cannot reasonably be questioned." Fed. R. Evid. 201(b)(2).

8. Based upon the foregoing, I respectfully submit the attached documents as exhibits to the Memorandum in Support of Defendants' Motion to Dismiss Plaintiffs' Complaint.

for the avoidance of confusion, I refer to the two French defendants by the names used for them in the Complaint: Sanofi S.A. and Aventis Pharma S.A.

[2] FDA updates the Orange Book periodically and posts the current edition and monthly supplements on its website. The full 2020 edition of the Orange Book, as it appeared on FDA's website, was digitally archived by the Wayback Machine and is available at this hyperlink.

9. I certify and attest that the foregoing statements made by me are true. I am aware that if any of the foregoing statements made by me are false, I am subject to punishment.

Dated: September 15, 2023

Respectfully submitted,

/s/ *Aaron Healey*

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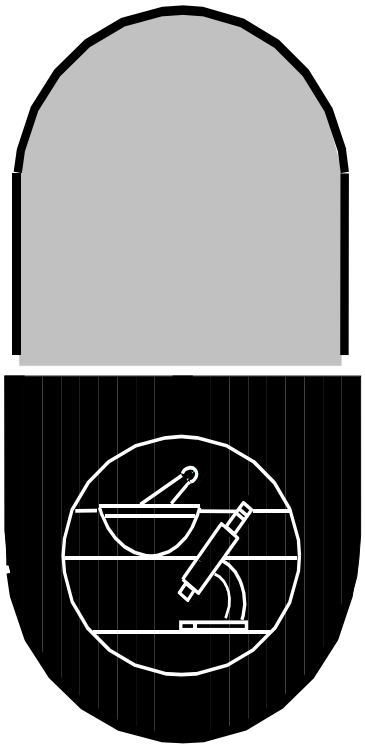
EXHIBIT A



APPROVED DRUG PRODUCTS

WITH

THERAPEUTIC EQUIVALENCE EVALUATIONS

40th EDITION

THE PRODUCTS IN THIS LIST HAVE BEEN APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
OFFICE OF MEDICAL PRODUCTS AND TOBACCO
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS
OFFICE OF GENERIC DRUG POLICY

2020

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

MYLAN

* MYLAN PHARMACEUTICALS
FENOFIBRATE, FENOFIBRATE
METOPROLOL TARTRATE AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
TRANEXAMIC ACID, TRANEXAMIC ACID

* MYLAN PHARMACEUTICALS INC
ABIRATERONE ACETATE, ABIRATERONE ACETATE
ACAMPROSATE CALCIUM, ACAMPROSATE CALCIUM
ACEBUTOLOL HYDROCHLORIDE, ACEBUTOLOL HYDROCHLORIDE
ACITRETIN, ACITRETIN
ALBUTEROL SULFATE, ALBUTEROL SULFATE
ALLOPURINOL, ALLOPURINOL
ALMOTRIPTAN MALATE, ALMOTRIPTAN MALATE
ALPRAZOLAM, ALPRAZOLAM
AMBRISENTAN, AMBRISENTAN
AMILORIDE HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE, AMILORIDE HYDROCHLORIDE
AMITRIPTYLINE HYDROCHLORIDE, AMITRIPTYLINE HYDROCHLORIDE
AMLODIPINE BESYLATE AND ATORVASTATIN CALCIUM, AMLODIPINE BESYLATE
AMLODIPINE BESYLATE AND VALSARTAN, AMLODIPINE BESYLATE
AMLODIPINE BESYLATE, AMLODIPINE BESYLATE
ANASTROZOLE, ANASTROZOLE
APIXABAN, APIXABAN
ATAZANAVIR SULFATE, ATAZANAVIR SULFATE
ATENOLOL AND CHLORTHALIDONE, ATENOLOL
ATENOLOL, ATENOLOL
ATOVAQUONE AND PROGUANIL HYDROCHLORIDE, ATOVAQUONE
AVITA, TRETINOIN
AZATHIOPRINE, AZATHIOPRINE
AZITHROMYCIN, AZITHROMYCIN
BACLOFEN, BACLOFEN
BENAZEPRIL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE, BENAZEPRIL HYDROCHLORIDE
BENAZEPRIL HYDROCHLORIDE, BENAZEPRIL HYDROCHLORIDE
BEPOTASTINE BESILATE, BEPOTASTINE BESILATE
BICALUTAMIDE, BICALUTAMIDE
BOSENTAN, BOSENTAN
BROMFENAC SODIUM, BROMFENAC SODIUM
BROMOCRIPTINE MESYLATE, BROMOCRIPTINE MESYLATE
BUDESONIDE, BUDESONIDE
BUPROPION HYDROCHLORIDE, BUPROPION HYDROCHLORIDE
BUSPIRONE HYDROCHLORIDE, BUSPIRONE HYDROCHLORIDE
BUTORPHANOL TARTRATE, BUTORPHANOL TARTRATE
CABERGOLINE, CABERGOLINE
CANDESARTAN CILEXETIL AND HYDROCHLOROTHIAZIDE, CANDESARTAN CILEXETIL
CANDESARTAN CILEXETIL, CANDESARTAN CILEXETIL
CAPECITABINE, CAPECITABINE
CAPTOPRIL AND HYDROCHLOROTHIAZIDE, CAPTOPRIL
CAPTOPRIL, CAPTOPRIL
CARBIDOPA AND LEVODOPA, CARBIDOPA
CARVEDILOL, CARVEDILOL
CELECOXIB, CELECOXIB
CETIRIZINE HYDROCHLORIDE ALLERGY, CETIRIZINE HYDROCHLORIDE (OTC)
CETIRIZINE HYDROCHLORIDE HIVES, CETIRIZINE HYDROCHLORIDE (OTC)
CHLOROTHIAZIDE, CHLOROTHIAZIDE
CHLORTHALIDONE, CHLORTHALIDONE
CIMETIDINE, CIMETIDINE
CINACALCET HYDROCHLORIDE, CINACALCET HYDROCHLORIDE
CIPROFLOXACIN HYDROCHLORIDE, CIPROFLOXACIN HYDROCHLORIDE
CITALOPRAM HYDROBROMIDE, CITALOPRAM HYDROBROMIDE
CLOBAZAM, CLOBAZAM
CLOBETASOL PROPIONATE, CLOBETASOL PROPIONATE
CLOMIPRAMINE HYDROCHLORIDE, CLOMIPRAMINE HYDROCHLORIDE
CLONAZEPAM, CLONAZEPAM
CLONIDINE HYDROCHLORIDE, CLONIDINE HYDROCHLORIDE
CLORAZEPATE DIPOTASSIUM, CLORAZEPATE DIPOTASSIUM
CLOZAPINE, CLOZAPINE

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

* MYLAN PHARMACEUTICALS INC
COLCHICINE, COLCHICINE
CYSTAGON, CYSTEAMINE BITARTRATE
DENAVIR, PENCICLOVIR
DESMOPRESSIN ACETATE, DESMOPRESSIN ACETATE
DESVENLAFAXINE SUCCINATE, DESVENLAFAXINE SUCCINATE
DEXMETHYLPHENIDATE HYDROCHLORIDE, DEXMETHYLPHENIDATE HYDROCHLORIDE
DEXTROAMP SACCHARATE, AMP ASPARTATE, DEXTROAMP SULFATE AND AMP SULFATE, AMPHETAMINE
DIAZEPAM, DIAZEPAM
DICLOFENAC POTASSIUM, DICLOFENAC POTASSIUM
DICLOFENAC SODIUM, DICLOFENAC SODIUM
DICYCLOMINE HYDROCHLORIDE, DICYCLOMINE HYDROCHLORIDE
DILTIAZEM HYDROCHLORIDE, DILTIAZEM HYDROCHLORIDE
DIPHENOXYLATE HYDROCHLORIDE AND ATROPINE SULFATE, ATROPINE SULFATE
DIVALPROEX SODIUM, DIVALPROEX SODIUM
DONEPEZIL HYDROCHLORIDE, DONEPEZIL HYDROCHLORIDE
DOXAZOSIN MESYLATE, DOXAZOSIN MESYLATE
DOXYCYCLINE HYCLATE, DOXYCYCLINE HYCLATE
ECONAZOLE NITRATE, ECONAZOLE NITRATE
EFAVIRENZ, EFAVIRENZ
ELETRIPTAN HYDROBROMIDE, ELETRIPTAN HYDROBROMIDE
ELIMITE, PERMETHRIN
EMTRICITABINE AND TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE
ENALAPRIL MALEATE AND HYDROCHLOROTHIAZIDE, ENALAPRIL MALEATE
ENTECAVIR, ENTECAVIR
EPLERENONE, EPLERENONE
ERLOTINIB HYDROCHLORIDE, ERLOTINIB HYDROCHLORIDE
ERYGEL, ERYTHROMYCIN
ESOMEPRAZOLE MAGNESIUM, ESOMEPRAZOLE MAGNESIUM
ESOMEPRAZOLE MAGNESIUM, ESOMEPRAZOLE MAGNESIUM (OTC)
ESTRADIOL, ESTRADIOL
ESTROPIPATE, ESTROPIPATE
ETOPOSIDE, ETOPOSIDE
EVOCLIN, CLINDAMYCIN PHOSPHATE
EXEMESTANE, EXEMESTANE
EXTENDED PHENYTOIN SODIUM, PHENYTOIN SODIUM
EXTINA, KETOCONAZOLE
EZETIMIBE, EZETIMIBE
FAMCICLOVIR, FAMCICLOVIR
FAMOTIDINE, FAMOTIDINE
FAMOTIDINE, FAMOTIDINE (OTC)
FEBUXOSTAT, FEBUXOSTAT
FENOFIBRATE, FENOFIBRATE
FEXOFENADINE HYDROCHLORIDE ALLERGY, FEXOFENADINE HYDROCHLORIDE (OTC)
FEXOFENADINE HYDROCHLORIDE HIVES, FEXOFENADINE HYDROCHLORIDE (OTC)
FEXOFENADINE HYDROCHLORIDE, FEXOFENADINE HYDROCHLORIDE
FLUCONAZOLE, FLUCONAZOLE
FLUOROURACIL, FLUOROURACIL
FLUOXETINE HYDROCHLORIDE, FLUOXETINE HYDROCHLORIDE
FLUPHENAZINE HYDROCHLORIDE, FLUPHENAZINE HYDROCHLORIDE
FLURBIPROFEN, FLURBIPROFEN
FOSAMPRENAVIR CALCIUM, FOSAMPRENAVIR CALCIUM
FROVATRIPTAN SUCCINATE, FROVATRIPTAN SUCCINATE
FUROSEMIDE, FUROSEMIDE
GABAPENTIN, GABAPENTIN
GATIFLOXACIN, GATIFLOXACIN
GLATIRAMER ACETATE, GLATIRAMER ACETATE
GLIMEPIRIDE, GLIMEPIRIDE
GLIPIZIDE, GLIPIZIDE
GLYBURIDE (MICRONIZED), GLYBURIDE
GRANISETRON HYDROCHLORIDE, GRANISETRON HYDROCHLORIDE
GUANFACINE HYDROCHLORIDE, GUANFACINE HYDROCHLORIDE
HALCINONIDE, HALCINONIDE
HALOPERIDOL, HALOPERIDOL
HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

* MYLAN PHARMACEUTICALS INC
HYDROXYCHLOROQUINE SULFATE, HYDROXYCHLOROQUINE SULFATE
IMATINIB MESYLATE, IMATINIB MESYLATE
INDAPAMIDE, INDAPAMIDE
INDOMETHACIN, INDOMETHACIN
KETOCONAZOLE, KETOCONAZOLE
KETOPROFEN, KETOPROFEN
KETOROLAC TROMETHAMINE, KETOROLAC TROMETHAMINE
LAMOTRIGINE, LAMOTRIGINE
LANSOPRAZOLE, LANSOPRAZOLE
LANSOPRAZOLE, LANSOPRAZOLE (OTC)
LEVETIRACETAM, LEVETIRACETAM
LEVOTHYROXINE SODIUM, LEVOTHYROXINE SODIUM **
LITHIUM CARBONATE, LITHIUM CARBONATE
LOPERAMIDE HYDROCHLORIDE, LOPERAMIDE HYDROCHLORIDE
LORATADINE, LORATADINE (OTC)
LORAZEPAM, LORAZEPAM
LOSARTAN POTASSIUM AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
LOSARTAN POTASSIUM, LOSARTAN POTASSIUM
LOXAPINE SUCCINATE, LOXAPINE SUCCINATE
LUXIQ, BETAMETHASONE VALERATE
MAPROTILINE HYDROCHLORIDE, MAPROTILINE HYDROCHLORIDE
MECLOFENAMATE SODIUM, MECLOFENAMATE SODIUM
MEMANTINE HYDROCHLORIDE, MEMANTINE HYDROCHLORIDE
MENTAX, BUTENAFINE HYDROCHLORIDE
MERCAPTOPURINE, MERCAPTOPURINE
MESALAMINE, MESALAMINE
METFORMIN HYDROCHLORIDE, METFORMIN HYDROCHLORIDE
METHIMAZOLE, METHIMAZOLE
METHOTREXATE SODIUM, METHOTREXATE SODIUM
METHYLDOPA AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
METHYLDOPA, METHYLDOPA
METHYLPHENIDATE HYDROCHLORIDE, METHYLPHENIDATE HYDROCHLORIDE
METOLAZONE, METOLAZONE
METOPROLOL TARTRATE, METOPROLOL TARTRATE
MINOCYCLINE HYDROCHLORIDE, MINOCYCLINE HYDROCHLORIDE
MIRTAZAPINE, MIRTAZAPINE
MYCOPHENOLATE MOFETIL, MYCOPHENOLATE MOFETIL
MYCOPHENOLIC ACID, MYCOPHENOLIC ACID
NADOLOL, NADOLOL
NAPROXEN, NAPROXEN
NEVIRAPINE, NEVIRAPINE
NIACIN, NIACIN
NICARDIPINE HYDROCHLORIDE, NICARDIPINE HYDROCHLORIDE
NIFEDIPINE, NIFEDIPINE
NISOLDIPINE, NISOLDIPINE
NITROFURANTOIN (MONOHYDRATE/MACROCRYSTALS), NITROFURANTOIN
OLANZAPINE, OLANZAPINE
OLMESARTAN MEDOXOMIL, OLMESARTAN MEDOXOMIL
OLOPATADINE HYDROCHLORIDE, OLOPATADINE HYDROCHLORIDE
OLUX E, CLOBETASOL PROPIONATE
OLUX, CLOBETASOL PROPIONATE
OMEPRAZOLE, OMEPRAZOLE
ONDANSETRON HYDROCHLORIDE, ONDANSETRON HYDROCHLORIDE
ONDANSETRON, ONDANSETRON
PALIPERIDONE, PALIPERIDONE
PAROXETINE HYDROCHLORIDE, PAROXETINE HYDROCHLORIDE
PERPHENAZINE AND AMITRIPTYLINE HYDROCHLORIDE, AMITRIPTYLINE HYDROCHLORIDE
PERPHENAZINE, PERPHENAZINE
PHENYTEK, PHENYTOIN SODIUM
POLYETHYLENE GLYCOL 3350, POLYETHYLENE GLYCOL 3350 (OTC)
POTASSIUM CHLORIDE, POTASSIUM CHLORIDE
PRAMIPEXOLE DIHYDROCHLORIDE, PRAMIPEXOLE DIHYDROCHLORIDE
PRASUGREL, PRASUGREL HYDROCHLORIDE
PRAZOSIN HYDROCHLORIDE, PRAZOSIN HYDROCHLORIDE

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

* MYLAN PHARMACEUTICALS INC
PREDNISONE, PREDNISONE
PREGABALIN, PREGABALIN
PROBENECID, PROBENECID
PROCHLORPERAZINE MALEATE, PROCHLORPERAZINE MALEATE
PROPAFENONE HYDROCHLORIDE, PROPAFENONE HYDROCHLORIDE
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
PROPRANOLOL HYDROCHLORIDE, PROPRANOLOL HYDROCHLORIDE
QUINAPRIL HYDROCHLORIDE, QUINAPRIL HYDROCHLORIDE
RASAGILINE MESYLATE, RASAGILINE MESYLATE
RISPERIDONE, RISPERIDONE
ROPINIROLE HYDROCHLORIDE, ROPINIROLE HYDROCHLORIDE
SILDENAFIL CITRATE, SILDENAFIL CITRATE
SOTALOL HYDROCHLORIDE, SOTALOL HYDROCHLORIDE
SPIRONOLACTONE AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
SPIRONOLACTONE, SPIRONOLACTONE
SULINDAC, SULINDAC
SUMATRIPTAN AND NAPROXEN SODIUM, NAPROXEN SODIUM
SUMATRIPTAN SUCCINATE, SUMATRIPTAN SUCCINATE
SYMFI LO, EFAVIRENZ
TACROLIMUS, TACROLIMUS
TADALAFIL, TADALAFIL
TAMOXIFEN CITRATE, TAMOXIFEN CITRATE
TELMISARTAN AND AMLODIPINE, AMLODIPINE BESYLATE
TELMISARTAN AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
TELMISARTAN, TELMISARTAN
TEMAZEPAM, TEMAZEPAM
TENOFOVIR DISOPROXIL FUMARATE, TENOFOVIR DISOPROXIL FUMARATE
TERAZOSIN HYDROCHLORIDE, TERAZOSIN HYDROCHLORIDE
TETRABENAZINE, TETRABENAZINE
THIORIDAZINE HYDROCHLORIDE, THIORIDAZINE HYDROCHLORIDE
THIOTHIXENE, THIOTHIXENE
TIMOLOL MALEATE, TIMOLOL MALEATE
TIZANIDINE HYDROCHLORIDE, TIZANIDINE HYDROCHLORIDE
TOBRAMYCIN, TOBRAMYCIN
TOLMETIN SODIUM, TOLMETIN SODIUM
TOLTERODINE TARTRATE, TOLTERODINE TARTRATE
TRAMADOL HYDROCHLORIDE AND ACETAMINOPHEN, ACETAMINOPHEN
TRAMADOL HYDROCHLORIDE, TRAMADOL HYDROCHLORIDE
TRAVOPROST, TRAVOPROST
TRETINOIN, TRETINOIN
TRIAMCINOLONE ACETONIDE, TRIAMCINOLONE ACETONIDE
TRIAMTERENE AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
TRIFLUOPERAZINE HYDROCHLORIDE, TRIFLUOPERAZINE HYDROCHLORIDE
TRILYTE, POLYETHYLENE GLYCOL 3350
URSODIOL, URSODIOL
VALSARTAN, VALSARTAN
VENLAFAXINE HYDROCHLORIDE, VENLAFAXINE HYDROCHLORIDE
VERAPAMIL HYDROCHLORIDE, VERAPAMIL HYDROCHLORIDE
VUSION, MICONAZOLE NITRATE
WIXELA INHUB, FLUTICASONE PROPIONATE
ZOLMITRIPTAN, ZOLMITRIPTAN
ZOLPIDEM TARTRATE, ZOLPIDEM TARTRATE
ZONALON, DOXEPIN HYDROCHLORIDE
ZOVIRAX, ACYCLOVIR

MYLAN ASI

* MYLAN ASI LLC
ACETAZOLAMIDE SODIUM, ACETAZOLAMIDE SODIUM
ADENOSINE, ADENOSINE
AZITHROMYCIN, AZITHROMYCIN
GRANISETRON HYDROCHLORIDE, GRANISETRON HYDROCHLORIDE
METOPROLOL TARTRATE, METOPROLOL TARTRATE
MIDAZOLAM HYDROCHLORIDE PRESERVATIVE FREE, MIDAZOLAM HYDROCHLORIDE
POLYMYXIN B SULFATE, POLYMYXIN B SULFATE
ROPIVACAINE HYDROCHLORIDE, ROPIVACAINE HYDROCHLORIDE

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

* MYLAN ASI LLC
SUMATRIPTAN SUCCINATE, SUMATRIPTAN SUCCINATE

MYLAN INSTITUTIONAL

* MYLAN INSTITUTIONAL INC
MYLERAN, BUSULFAN
SULFAMYLON, MAFENIDE ACETATE
* MYLAN INSTITUTIONAL LLC
ALOPRIM, ALLOPURINOL SODIUM
AMIODARONE HYDROCHLORIDE, AMIODARONE HYDROCHLORIDE
ARGATROBAN, ARGATROBAN
AZACITIDINE, AZACITIDINE
BIVALIRUDIN, BIVALIRUDIN
CHLOROTHIAZIDE SODIUM, CHLOROTHIAZIDE SODIUM
CIDOFOVIR, CIDOFOVIR
COSYNTROPIN, COSYNTROPIN
DEXMEDETOMIDINE HYDROCHLORIDE, DEXMEDETOMIDINE HYDROCHLORIDE
DEXRAZOXANE HYDROCHLORIDE, DEXRAZOXANE HYDROCHLORIDE
DIPHENHYDRAMINE HYDROCHLORIDE, DIPHENHYDRAMINE HYDROCHLORIDE
DURACLON, CLONIDINE HYDROCHLORIDE
ESMOLOL HYDROCHLORIDE, ESMOLOL HYDROCHLORIDE
ETHACRYNATE SODIUM, ETHACRYNATE SODIUM
FOMEPIZOLE, FOMEPIZOLE
FULVESTRANT, FULVESTRANT
HYDRALAZINE HYDROCHLORIDE, HYDRALAZINE HYDROCHLORIDE
IBUTILIDE FUMARATE, IBUTILIDE FUMARATE
ISOSULFAN BLUE, ISOSULFAN BLUE
KETAMINE HYDROCHLORIDE, KETAMINE HYDROCHLORIDE
MEFOXIN IN PLASTIC CONTAINER, CEFOXITIN SODIUM
MELPHALAN HYDROCHLORIDE, MELPHALAN HYDROCHLORIDE
METHADONE HYDROCHLORIDE, METHADONE HYDROCHLORIDE
METHOCARBAMOL, METHOCARBAMOL
NALOXONE HYDROCHLORIDE, NALOXONE HYDROCHLORIDE
OCTREOTIDE ACETATE (PRESERVATIVE FREE), OCTREOTIDE ACETATE
PALONOSETRON HYDROCHLORIDE, PALONOSETRON HYDROCHLORIDE
RIMSO-50, DIMETHYL SULFOXIDE
ROCURONIUM BROMIDE, ROCURONIUM BROMIDE
SOTRADECOL, SODIUM TETRADECYL SULFATE
THIAMINE HYDROCHLORIDE, THIAMINE HYDROCHLORIDE
TRANEXAMIC ACID, TRANEXAMIC ACID
ULTIVA, REMIFENTANIL HYDROCHLORIDE

MYLAN IRELAND LTD

* MYLAN IRELAND LTD
ARIXTRA, FONDAPARINUX SODIUM
MIACALCIN, CALCITONIN SALMON
PRETOMANID, PRETOMANID
YUPELRI, REVEFENACIN

MYLAN LABS

* MYLAN LABORATORIES LTD
NEVIRAPINE, NEVIRAPINE

MYLAN LABS LTD

* MYLAN LABORATORIES LTD
ADENOSINE, ADENOSINE
AMIFOSTINE, AMIFOSTINE
AMPICILLIN AND SULBACTAM, AMPICILLIN SODIUM
AMPICILLIN SODIUM, AMPICILLIN SODIUM
AZITHROMYCIN, AZITHROMYCIN
BACLOFEN, BACLOFEN
BUSULFAN, BUSULFAN
CAPREOMYCIN SULFATE, CAPREOMYCIN SULFATE
CASPOFUNGIN ACETATE, CASPOFUNGIN ACETATE
CIMDUO, LAMIVUDINE
CLADRIBINE, CLADRIBINE
CLINDAMYCIN PHOSPHATE, CLINDAMYCIN PHOSPHATE
CLOFARABINE, CLOFARABINE
CYANOCOBALAMIN, CYANOCOBALAMIN

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

* MYLAN LABORATORIES LTD
CYTARABINE, CYTARABINE
DACTINOMYCIN, DACTINOMYCIN
DAPTOMYCIN, DAPTOMYCIN
DESOGESTREL AND ETHINYL ESTRADIOL, DESOGESTREL
DEXAMETHASONE SODIUM PHOSPHATE, DEXAMETHASONE SODIUM PHOSPHATE
DOCETAXEL, DOCETAXEL
DOCETAXEL, DOCETAXEL
DOXORUBICIN HYDROCHLORIDE, DOXORUBICIN HYDROCHLORIDE
DOXYCYCLINE, DOXYCYCLINE HYCLATE
DROSPIRENONE AND ETHINYL ESTRADIOL, DROSPIRENONE
EPTIFIBATIDE, EPTIFIBATIDE
ESMOLOL HYDROCHLORIDE, ESMOLOL HYDROCHLORIDE
ESOMEPRAZOLE SODIUM, ESOMEPRAZOLE SODIUM
ESTRADIOL AND NORETHINDRONE ACETATE, ESTRADIOL
ETHYNODIOL DIACETATE AND ETHINYL ESTRADIOL, ETHINYL ESTRADIOL
ETOMIDATE, ETOMIDATE
ETOPOSIDE, ETOPOSIDE
FAMOTIDINE PRESERVATIVE FREE, FAMOTIDINE
FAMOTIDINE, FAMOTIDINE
FLUDARABINE PHOSPHATE, FLUDARABINE PHOSPHATE
FLUMAZENIL, FLUMAZENIL
FLUOROURACIL, FLUOROURACIL
FLUPHENAZINE DECANOATE, FLUPHENAZINE DECANOATE
FOSAPREPITANT DIMEGLUMINE, FOSAPREPITANT DIMEGLUMINE
FOSPHENYTOIN SODIUM, FOSPHENYTOIN SODIUM
GANCICLOVIR SODIUM, GANCICLOVIR SODIUM
GEMCITABINE HYDROCHLORIDE, GEMCITABINE HYDROCHLORIDE
GRANISETRON HYDROCHLORIDE, GRANISETRON HYDROCHLORIDE
HALOPERIDOL DECANOATE, HALOPERIDOL DECANOATE
HALOPERIDOL, HALOPERIDOL LACTATE
HEPARIN SODIUM, HEPARIN SODIUM
IBANDRONATE SODIUM, IBANDRONATE SODIUM
LAMIVUDINE, LAMIVUDINE
LEUCOVORIN CALCIUM PRESERVATIVE FREE, LEUCOVORIN CALCIUM
LEVETIRACETAM, LEVETIRACETAM
LEVOFLOXACIN, LEVOFLOXACIN
LEVONORGESTREL AND ETHINYL ESTRADIOL AND ETHINYL ESTRADIOL, ETHINYL ESTRADIOL
LEVONORGESTREL AND ETHINYL ESTRADIOL, ETHINYL ESTRADIOL
LEVONORGESTREL, LEVONORGESTREL
LEVONORGESTREL, LEVONORGESTREL (OTC)
LINEZOLID, LINEZOLID
MAGNESIUM SULFATE IN DEXTROSE 5% IN PLASTIC CONTAINER, MAGNESIUM SULFATE
MAGNESIUM SULFATE IN PLASTIC CONTAINER, MAGNESIUM SULFATE
MEDROXYPROGESTERONE ACETATE, MEDROXYPROGESTERONE ACETATE
METHOTREXATE SODIUM PRESERVATIVE FREE, METHOTREXATE SODIUM
METRONIDAZOLE IN PLASTIC CONTAINER, METRONIDAZOLE
MITOMYCIN, MITOMYCIN
MOXIFLOXACIN HYDROCHLORIDE IN SODIUM CHLORIDE 0.8% IN PLASTIC CONTAINER, MOXIFLOXACIN
MYCOPHENOLATE MOFETIL HYDROCHLORIDE, MYCOPHENOLATE MOFETIL HYDROCHLORIDE
NALBUPHINE HYDROCHLORIDE, NALBUPHINE HYDROCHLORIDE
NOREPINEPHRINE BITARTRATE, NOREPINEPHRINE BITARTRATE
NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL AND FERROUS FUMARATE, ETHINYL ESTRADIOL
NORETHINDRONE ACETATE AND ETHINYL ESTRADIOL, ETHINYL ESTRADIOL
NORETHINDRONE ACETATE, NORETHINDRONE ACETATE
NORETHINDRONE AND ETHINYL ESTRADIOL AND FERROUS FUMARATE, ETHINYL ESTRADIOL
NORETHINDRONE, NORETHINDRONE
NORGESTIMATE AND ETHINYL ESTRADIOL, ETHINYL ESTRADIOL
ONDANSETRON HYDROCHLORIDE, ONDANSETRON HYDROCHLORIDE
OXALIPLATIN, OXALIPLATIN
PACLITAXEL, PACLITAXEL
PAMIDRONATE DISODIUM, PAMIDRONATE DISODIUM
PARICALCITOL, PARICALCITOL
PIPERACILLIN AND TAZOBACTAM, PIPERACILLIN SODIUM
PROCHLORPERAZINE EDISYLATE, PROCHLORPERAZINE EDISYLATE

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

* MYLAN LABORATORIES LTD
RANITIDINE HYDROCHLORIDE, RANITIDINE HYDROCHLORIDE
RIFAMPIN, RIFAMPIN
SODIUM NITROPRUSSIDE, SODIUM NITROPRUSSIDE
SULFAMETHOXAZOLE AND TRIMETHOPRIM, SULFAMETHOXAZOLE
SYMFI, EFAVIRENZ
TOBRAMYCIN SULFATE, TOBRAMYCIN SULFATE
TOPOTECAN HYDROCHLORIDE, TOPOTECAN HYDROCHLORIDE
VANCOMYCIN HYDROCHLORIDE, VANCOMYCIN HYDROCHLORIDE
VECURONIUM BROMIDE, VECURONIUM BROMIDE
ZOLEDRONIC ACID, ZOLEDRONIC ACID

MYLAN PHARMS INC

* MYLAN PHARMACEUTICALS INC
ABACAVIR SULFATE, ABACAVIR SULFATE
ACYCLOVIR, ACYCLOVIR
AMNESTEEM, ISOTRETINOIN
ARMODAFINIL, ARMODAFINIL
ATORVASTATIN CALCIUM, ATORVASTATIN CALCIUM
AVITA, TRETINOIN
BACLOFEN, BACLOFEN
CHLORDIAZEPOXIDE AND AMITRIPTYLINE HYDROCHLORIDE, AMITRIPTYLINE HYDROCHLORIDE
CLINDAMYCIN PHOSPHATE AND BENZOYL PEROXIDE, BENZOYL PEROXIDE
CYCLOBENZAPRINE HYDROCHLORIDE, CYCLOBENZAPRINE HYDROCHLORIDE
DICLOFENAC SODIUM, DICLOFENAC SODIUM
DIGOXIN, DIGOXIN
DONEPEZIL HYDROCHLORIDE, DONEPEZIL HYDROCHLORIDE
DOXEPIN HYDROCHLORIDE, DOXEPIN HYDROCHLORIDE
DOXYCYCLINE, DOXYCYCLINE
EPROSARTAN MESYLATE, EPROSARTAN MESYLATE
ESZOPICLONE, ESZOPICLONE
FENOFIBRATE (MICRONIZED), FENOFIBRATE
FENOFIBRATE, FENOFIBRATE
FLURAZEPAM HYDROCHLORIDE, FLURAZEPAM HYDROCHLORIDE
GABAPENTIN, GABAPENTIN
HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
ITRACONAZOLE, ITRACONAZOLE
LANSOPRAZOLE, LANSOPRAZOLE
LITHIUM CARBONATE, LITHIUM CARBONATE
MAXZIDE, HYDROCHLOROTHIAZIDE
MAXZIDE-25, HYDROCHLOROTHIAZIDE
MECLIZINE HYDROCHLORIDE, MECLIZINE HYDROCHLORIDE
METFORMIN HYDROCHLORIDE, METFORMIN HYDROCHLORIDE
METOPROLOL SUCCINATE, METOPROLOL SUCCINATE
MIDODRINE HYDROCHLORIDE, MIDODRINE HYDROCHLORIDE
MODAFINIL, MODAFINIL
NABUMETONE, NABUMETONE
NEVIRAPINE, NEVIRAPINE
PANTOPRAZOLE SODIUM, PANTOPRAZOLE SODIUM
PHENYTOIN, PHENYTOIN
PINDOLOL, PINDOLOL
PIOGLITAZONE HYDROCHLORIDE, PIOGLITAZONE HYDROCHLORIDE
PRAVASTATIN SODIUM, PRAVASTATIN SODIUM
PREDNISOLONE SODIUM PHOSPHATE, PREDNISOLONE SODIUM PHOSPHATE
RILUZOLE, RILUZOLE
RIZATRIPTAN BENZOATE, RIZATRIPTAN BENZOATE
SILDENAFIL CITRATE, SILDENAFIL CITRATE
TIZANIDINE HYDROCHLORIDE, TIZANIDINE HYDROCHLORIDE
TOLAZAMIDE, TOLAZAMIDE
TOLBUTAMIDE, TOLBUTAMIDE
TOLTERODINE TARTRATE, TOLTERODINE TARTRATE
TRIAZOLAM, TRIAZOLAM
VALACYCLOVIR HYDROCHLORIDE, VALACYCLOVIR HYDROCHLORIDE
VALSARTAN AND HYDROCHLOROTHIAZIDE, HYDROCHLOROTHIAZIDE
VORICONAZOLE, VORICONAZOLE
ZIDOVUDINE, ZIDOVUDINE

APPENDIX B - PRODUCT NAME SORTED BY APPLICANT

** M **

* MYLAN PHARMACEUTICALS INC.
FLUVASTATIN SODIUM, FLUVASTATIN SODIUM
NIZATIDINE, NIZATIDINE
OXYBUTYNIN CHLORIDE, OXYBUTYNIN CHLORIDE

MYLAN SPECIALITY LP

* MYLAN SPECIALTY LP
ACCUNEB, ALBUTEROL SULFATE
ANADROL-50, OXYMETHOLONE
ASTELIN, AZELASTINE HYDROCHLORIDE
ASTEPRO, AZELASTINE HYDROCHLORIDE
AVC, SULFANILAMIDE
BUTISOL SODIUM, BUTABARBITAL SODIUM
CESAMET, NABILONE
COLYTE WITH FLAVOR PACKS, POLYETHYLENE GLYCOL 3350
CORTIFOAM, HYDROCORTISONE ACETATE
DEMADEX, TORSEMIDE
DEPEN, PENICILLAMINE
DIPENTUM, OLSALAZINE SODIUM
DYMISTA, AZELASTINE HYDROCHLORIDE
EDLUAR, ZOLPIDEM TARTRATE
ELESTRIN, ESTRADIOL
EPIFOAM, HYDROCORTISONE ACETATE
EPIPEN JR., EPINEPHRINE
EPIPEN, EPINEPHRINE
FELBATOL, FELBAMATE
GASTROCROM, CROMOLYN SODIUM
LEVALBUTEROL HYDROCHLORIDE, LEVALBUTEROL HYDROCHLORIDE
MUSE, ALPROSTADIL
PROCTOFOAM HC, HYDROCORTISONE ACETATE
ROWASA, MESALAMINE
SFROWASA, MESALAMINE
SOMA, CARISOPRODOL
TOBI PODHALER, TOBRAMYCIN
TOBI, TOBRAMYCIN

MYLAN SPECLT

* MYLAN SPECIALTY LP
PERFOROMIST, FORMOTEROL FUMARATE

MYLAN TECHNOLOGIES

* MYLAN TECHNOLOGIES INC
BUPRENORPHINE HYDROCHLORIDE AND NALOXONE HYDROCHLORIDE, BUPRENORPHINE HYDROCHLORIDE
CLONIDINE, CLONIDINE
ESTRADIOL, ESTRADIOL
FENTANYL-100, FENTANYL
FENTANYL-12, FENTANYL
FENTANYL-25, FENTANYL
FENTANYL-37, FENTANYL
FENTANYL-50, FENTANYL
FENTANYL-62, FENTANYL
FENTANYL-75, FENTANYL
FENTANYL-87, FENTANYL
LIDOCAINE, LIDOCAINE
NITROGLYCERIN, NITROGLYCERIN
RIVASTIGMINE, RIVASTIGMINE
SCOPOLAMINE, SCOPOLAMINE
XULANE, ETHINYL ESTRADIOL

** N **

NAARI PTE LTD

* NAARI PTE LTD
LEVONORGESTREL, LEVONORGESTREL (OTC)
NORGESTIMATE AND ETHINYL ESTRADIOL, ETHINYL ESTRADIOL

NABRIVA

* NABRIVA THERAPEUTICS IRELAND DAC
XENLETA, LEFAMULIN ACETATE

NALPROPION

EXHIBIT B

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 105279

MEETING MINUTES

Mylan GmbH
Attention: Felix Siegel, Ph.D.
Senior Director, Head of Regulatory Affairs, Biologics
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Dr. Siegel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for insulin glargine injection (rDNA Origin), 100 IU/mL.

We also refer to the meeting between representatives of your firm and the FDA on March 7, 2014. The purpose of the meeting was to discuss regulatory, device, nonclinical, and clinical requirements to support further development.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Richard Whitehead, Regulatory Project Manager at (301) 796-4945.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B

Meeting Category: End of Phase 2

Meeting Date and Time: Friday, March 7, 2014, 1-2PM

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 105279

Product Name: insulin glargine injection (rDNA origin) 100 IU/mL

Indication: long- acting human insulin analog indicated to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus

Sponsor/Applicant Name: Mylan GmbH

Meeting Chair: Jean-Marc Guettier, M.D.

Meeting Recorder: Richard Whitehead, M.S.

FDA ATTENDEES

Office of New Drugs, Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Director (Acting)
Ali Mohamadi, M.D., Clinical Team Leader (Acting)
Hyon Kwon, Pharm.D, M.P.H., Clinical Reviewer
Miyun Tsai-Turton Ph.D., Nonclinical Reviewer
Karen Davis Bruno, Ph.D., Nonclinical Team Leader
Richard Whitehead, M.S., Regulatory Project Manager
Pamela Lucarelli, Chief Project Management Staff

Office of Biostatistics

Mark Rothmann, Ph.D., Biostatistics Team Leader
Jennifer Clark, Ph.D., Biostatistics Reviewer

Office of Clinical Pharmacology
Lokesh Jain, Ph.D., Clinical Pharmacology Team Leader
Suryanarayana Sista, Ph.D., Clinical Pharmacology Reviewer
Manoj Khurana, Ph.D., Clinical Pharmacology Reviewer

Office of New Drug Quality Assessment (ONDQA)
Su Tran, Ph.D., Product Quality Team Leader

Office of Combination Products
Patricia Love, M.D., MBA, Deputy Director
Bindi Nikhar, M.D., Associate Director

Center for Devices and Radiological Health (CDRH)
Catherine Li, M.S., Combination Products Reviewer
QuynhNhu Nguyen, M.S., Combination Products Human Factors Specialist
Patricia Beaston, M.D., Ph.D., Medical Officer

Office of Biotechnology Products
Daniela Verthelyi, Ph.D., Primary Reviewer

Division of Medication Error Prevention and Analysis
Sarah Vee, Pharm.D., Primary Reviewer

Office of Regulatory Policy
Janice Weiner, J.D., M.P.H., Senior Regulatory Counsel

SPONSOR ATTENDEES

Abhijit Barve, President, Research & Development and Regulatory Sciences, Biocon
Andrea B. Miller, Sr. Vice President, Global Complex Products Operations, Mylan
Bin Sun, Senior Lead Biostatistician, Mylan
Brian Stone, Global Counsel, Regulatory Affairs, Mylan
Felix Siegel, Sr. Director, Regulatory Affairs, Mylan
Jeffrey Smith, Vice President Pharmacology and Toxicology, Mylan
Libbie Mansell, Vice President, Regulatory Strategy, Biogenerics, Mylan
Michael Ankersen, Clinical Project Lead – Diabetes, Mylan
Raja Sekhar Reddy Vanga, Assistant General Manager, Regulatory Sciences, Biocon
Rajesh Ullanat, Associate Vice President, Technical Development, Mylan
Ramakrishnan M. S., General Manager, Research & Development, Biocon
Rasmus Rojkjaer, Vice President, Head of Global Biologics R&D, Mylan
Raymond Urbanski, Chief Medical Officer, Mylan
Sunil Jain, Associate Vice President – Program Head Insulin Analogues, Biocon
Walt Owens, Sr. Vice President, Global R&D, Mylan

1.0 BACKGROUND

Mylan states that the molecular structure of "Mylan Insulin glargine," solution for subcutaneous injection and Lantus (Sanofi; NDA 21081) is "identical." Mylan states that in both products insulin glargine consists of 53 amino acids arranged in two chains. The A chain (21 amino acids) and the B chain (32 amino acids) are connected by disulfide linkages. There are two differences in the amino acid sequence between human insulin and insulin glargine. The C-terminal of the B chain is elongated by two Arginine residues. The C-terminal Asparagine of the A chain is replaced by Glycine.

The indication and limitations of use are proposed to be the same as that in the labeling of Lantus.

Mylan Insulin glargine is a proposed long-acting human insulin analog for which Mylan is seeking an indication to improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus (T1DM) and in adults with type 2 diabetes mellitus (T2DM). Important Limitations of Use: Not recommended for treating diabetic ketoacidosis. Use intravenous, short-acting insulin instead.

The dosage form, route of administration and dosing regimen are proposed to be the same as for the listed drug relied upon (US-approved Lantus): Solution for injection 100 units/mL (U-100) in 10 mL vials and 3 mL Mylan pen, disposable insulin device.

Insulin glargine is an analogue of human insulin produced by recombinant DNA technology. Mylan, and its development partner, Biocon Ltd., are proposing to develop this product as a "substitutable, therapeutic equivalent" to Sanofi's Lantus. Lantus was approved on April 20, 2000. There are no currently marketed products identified in FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book) as therapeutically equivalent to Lantus, and Mylan states that the availability of a therapeutic equivalent would offer significant public health benefits in terms of patient access and health care cost containment. Biocon was the original sponsor for the referenced IND 105279. In February 2013, Mylan entered a co-development agreement with Biocon for insulin glargine. In August 2013, the sponsorship of the IND was transferred from Biocon to Mylan.

The following list provides an overview of the development program conducted to date to compare Mylan Insulin glargine and Lantus:

1. Physico-chemical characterization includes;
    - Primary structure;
    - Secondary structure;
    - Higher order structures;
    - Impurity profile including RP-HPLC and SEC techniques.

2. Biological characterization includes;
    - Biological activity with respect to glucose uptake, binding to insulin receptor, binding to IGF-1 receptor and cell proliferation in in-vitro studies.

3. Toxicokinetic and toxicology in non-clinical studies;

4. Pharmacokinetic and pharmacodynamic profiles in clinical studies;

5. Clinical effect and safety profile, including immunogenicity, in clinical studies;

6. Same operating principles for Mylan's delivery pen and Sanofi's Solostar.

Mylan intends to seek marketing approval for Mylan Insulin glargine injection under section 505(b)(2) and plans to rely on the Agency's previous finding of safety and effectiveness for the listed drug, Lantus.

The sponsor proposes to conduct two additional supportive clinical studies to confirm the therapeutic equivalence of Lantus and Mylan Insulin glargine:

- A 400-patient 52-week non-inferiority study in T1DM using Mylan disposable pens and Lantus disposable pens. The primary endpoint will be change in HbA1C from baseline at 24 weeks;
- A 500-patient 24- week non-inferiority study in T2DM study using Mylan disposable pens and Lantus disposable pens. The primary endpoint will be change in HbA1C from baseline at 24 weeks.

The purpose of the meeting was to discuss the acceptability of regulatory, CMC, device, non-clinical and clinical proposals to support the therapeutic equivalence of Mylan Insulin glargine to Lantus. In addition, Mylan was seeking concurrence on the design of the clinical studies to ensure data generated from these studies, assuming acceptable results, would be adequate to support product registration.

2.0 DISCUSSION

2.1 Regulatory

Question 1: Mylan Insulin glargine and Lantus are pharmaceutically equivalent. Bioequivalence was demonstrated in the completed PK/PD study (GLARGCT100111). Through additional studies Mylan will demonstrate that Mylan Insulin glargine and Lantus will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Mylan Insulin glargine and Lantus are therefore therapeutic equivalents (TE).

a. Given the analytical characterization data and completed PK/PD study, does the Agency agree that a 52-week safety, immunogenicity and efficacy study in T1DM patients, in combination with 24-week study in T2DM patients provides sufficient supportive evidence that Mylan Insulin glargine and Lantus will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling along with the completed BE (PK/PD study) and will therefore be considered therapeutically equivalent?

b. With regard to the optional study, does the Agency agree that the proposed 6-month switch extension study (optional study) in T2DM patients as described in Figure 1.6.2-3 is sufficient to provide additional supportive evidence that Mylan Insulin glargine and Lantus are therapeutically equivalent?

c. The formulation of Mylan Insulin glargine is identical to the Lantus formulation in prefilled pens. However, the Lantus vial contains (b) (4) Polysorbate-20, which was not present in the initially marketed Lantus vial product. Does the Agency agree that the slight difference in the formulation of the vial has no impact on the determination of TE?

d. Mylan assumes that, consistent with other TE determinations, a demonstration of TE between Mylan Insulin glargine and Lantus® will be reflected in AB-ratings in the Orange Book. Does the agency agree?

FDA Response to Question 1: **Your questions a, b, and d regarding the criteria for demonstrating therapeutic equivalence between your proposed Mylan Insulin glargine and US-approved Lantus require further internal Agency discussion. Although the background package makes several conclusory statements regarding the "pharmaceutical equivalence" and "bioequivalence" of these biological products, FDA notes that these determinations would be review issues, and the application of these terms to rDNA-derived protein products such as insulin glargine requires additional FDA consideration. Accordingly, while we can provide comments on whether the design of your proposed Phase 3 studies would be adequate to support your proposed 505(b)(2) application, we are unable to comment on whether the design of these studies, in conjunction with other data, would provide adequate data to support a determination of therapeutic equivalence.**

See our response to Question 9a below, which includes preliminary comments for your proposed Phase 3 studies (MYL-GAI-3001 and MYL-GAI-3002) based on the provided synopsis. Also see our response to Question 9b.

With respect to question c, the difference in the formulation of the Lantus vial compared to Mylan's insulin glargine would not be anticipated to impact a determination of TE if this difference does not affect the clinical effect and safety profile. However, this will be a review issue.

Question 1 Discussion: **The sponsor stated that it would like to continue the dialogue and work with the Agency to develop a product that is demonstrated to be "therapeutically equivalent" to Lantus. FDA reiterated that the approach to and criteria for a demonstration of "therapeutic equivalence" for rDNA-derived protein products such as insulin glargine require further discussion within the Agency.**

Question 2: Mylan intends to obtain marketing approval for Mylan Insulin glargine injection under section 505(b)(2) and plans to rely on the Agency's previous finding of safety and effectiveness for the listed drug, Lantus.

a. Does the Agency agree that no pediatric clinical studies are required to support pediatric dosing?

b. Does the Agency agree that the development of a pediatric formulation is not required?

FDA Response to Question 2: **Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.**

Because none of the criteria apply at this time to your application, your application does not trigger PREA. If there are any changes to your development plans that would cause your application to trigger PREA, your status would change.

Question 2 Discussion: **No additional discussion.**

2.2 Quality

Question 3: Mylan is currently manufacturing Mylan Insulin glargine at a facility located in Bangalore, India. Mylan is in the process of commissioning an additional drug substance (DS) and drug product (DP) manufacturing site in Malaysia to meet the global commercial demand. The three-way toxicity and three-way PK/PD studies were executed using Mylan Insulin glargine manufactured at the facility in India. Mylan Insulin glargine manufactured at the Indian facility will also be used for the planned clinical safety and efficacy studies. Mylan intends to include both facilities, in India and in Malaysia, as commercial manufacturing sites into the marketing application.

a. Does the Agency agree that data generated from clinical and animal toxicity studies for Mylan Insulin glargine manufactured in India in combination with physicochemical and biological data positively demonstrating acceptable comparability for the products manufactured at both sites provided at the time of submission of the marketing authorization are sufficient to support approval of commercial manufacturing in India and in Malaysia?

b. Does the Agency agree that the proposed approach is adequate to establish comparability between Mylan Insulin glargine manufactured in Malaysia and Mylan Insulin glargine manufactured in India?

c. Does the Agency agree that the physicochemical and biological studies comparing Mylan Insulin glargine manufactured in India with Lantus are adequate to support the approval

of the marketing application and that no additional studies are required comparing the product manufactured in Malaysia with reference product?

FDA Response to Question 3:

a. See the response to 3 b below.

b. Your proposed comparability plan would be adequate provided that the comparability report in the NDA will include information on both process- and product-related impurities as well as on product-related substances and their biological activities. The information will need to be supported by comparative impurity profiles (e.g., chromatograms, retention times, and numerical results). Additional nonclinical and/or clinical studies may be required in support of any difference in the information. Provide stability data to compare your drug product manufactured in India and in Malaysia, including long term and accelerated storage conditions, stress conditions such as forced degradation and photostability, and in-use conditions.

Other comments:

- **We remind you that the demonstration of comparability between the manufacturing sites in India and in Malaysia per ICH Guidance Q5E "Comparability of Biotechnological/Biological Products" would be acceptable provided that: these two sites are either your own facilities or your contract facilities and you have full access to all CMC information associated with both sites; this information will be submitted in your NDA (i.e., no Drug Master File will be submitted for either site); and the manufacturing processes at both sites starts with the same source material (i.e., working cell bank).**

- **Add a bioassay to the drug substance specification, and provide data to support the correlation of 0.036378 mg of insulin glargine being equal to 1 Unit of insulin glargine.**

- **If the differences between the manufacturing sites include any difference related to the pen injector, issues discussed in the response to questions 4 and 5 may be applicable.**

c. Assuming that comparability is demonstrated between your product (drug substance and drug product) manufactured in India and in Malaysia, a demonstration of similarity between your product (drug substance and drug product) manufactured in Malaysia and US-approved Lantus and E.U.-approved insulin glargine would not be required provided that your similarity testing program for your product manufactured in India and US-approved Lantus and E.U.-approved insulin glargine will include the same analytical testing proposed for the product comparability exercises conducted for the product (drug substance and

drug product) manufactured in India and in Malaysia. In addition, provide stability data to compare the degradation profiles of your drug product manufactured in India and those of US-approved Lantus and E.U.-approved insulin glargine, including accelerated storage conditions, stress conditions such as forced degradation and photostability, and in-use conditions.

Additional Comment: For the combination product, manufacturing facilities are subject to 21 CFR Part 4.

Question 3 Discussion: **The sponsor provided the following information to FDA's preliminary comments: Both facilities in India and Malaysia are Biocon facilities. No DMFs will be submitted in support of CMC site or manufacturing process, all CMC information will be submitted in the NDA. The working cell bank will be used at both sites. A bioassay based on USP<121> will be included in the drug substance specification. The detailed comparability protocol will be submitted to FDA for review. FDA acknowledged the sponsor's additional information and had no further comment.**

2.3 CDRH and CMC

Question 4: Mylan intends to use its prefilled pen in the clinical studies to support that Mylan Insulin glargine and Lantus will have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Comprehensive data on the prefilled pen will be provided in the IND submission.

Does the Agency agree that this information will be sufficient to support the use of the prefilled pen in the proposed clinical trials?

FDA Response to Question 4: **We have the following comments regarding the data to be provided on the prefilled pen:**

- **Please provide a complete and detailed description of your proposed device.**
- **As several materials are used in the manufacture of the final pen injector, please provide a complete list of materials such as base materials, polymers, colorants, adhesives, inks, etc., used in the subject device and their Material Safety Data Sheets or Technical Data Sheets for evaluation.**
- **You have stated that you will provide test results from dose accuracy testing in accordance with ISO 11608-1:2012 to confirm the device delivers an accurate dose. However, in order to support the use of the pen in a clinical study the full performance assessment of the pen device should be provided. Please refer to and follow ISO 11608-1:2012, ISO 11608-2:2012 and ISO 11608-3:2012. Please perform all recommended tests and submit all test results to the Agency.**

- **The proposed biocompatibility tests are adequate to evaluate the pen component of injection system.**
- **It is unclear if the needle to be used with the pen is a 510(k) cleared device. If so, please provide the 510(k) number. Otherwise, please perform the biocompatibility tests according to ISO 10993-1 standard.**
- **The barrel of the pen injector appears to have ink markings. Under some circumstances residues derived from marking the device barrel can cause contamination of the drug. This contamination may affect the drug component or cause unintended exposure to for the patient. Please provide study report to show that the ink marking do not show any penetration into the drug compartment to cause contamination.**
- **The proposed in-use stability strategy is acceptable. Also, we remind you to include stability data in the NDA to show that the long-term storage under refrigerated conditions will have no adverse impact on the performance of the pen injector.**

- **Regarding the usability tests during development of the prefilled pen, please see addition comments in response to question #5**

***Question 4 Discussion*: The sponsor acknowledged the Agency's request to complete ISO 11608-1:2012, ISO 11608-2:2012, ISO 11608-3:2012 prior to initiation of the clinical trial with the pre-filled pen. The Agency reiterated that the strategy should follow standards listed in FDA's response (above).**

Mylan confirmed that the needle used with the pen is a 510(k) device and that it will provide the 510(k) number to the IND. FDA asked the sponsor to confirm that the appropriate tests outlined in ISO 11608 (such as accuracy testing) include the proposed needle attached to the pen-injector to be marketed.

FDA noted the discussion of slide 8 shown by the sponsor at the meeting and Mylan provided the following explanation: the glass cartridge contains the drug and there is a gap in between the glass cartridge and cartridge holder; it is the cartridge holder that contains the ink markings, and there are no markings on the glass cartridge; due to the gap, studies for ink permeation or penetrations are not necessary. Mylan will notify the review division if there are changes to the described design made to the pre-filled pen (not changing the operating principles) after the clinical trials have been completed. Mylan asked whether the Agency would expect supportive clinical trials with this revised device beyond the human factor studies. FDA responded that, although this question focuses on the device constituent and not the clinical trials, it appears that Mylan plans to modify the device. FDA stated that sometimes even a minor change can affect the safety and effectiveness of the device, and any change to the device constituent part changes the combination product as a whole. Therefore, it is premature to

comment on the potential effects on the clinical trial program. If preliminary comments are sought, the sponsor should provide more details on the proposed modifications.

Finally, the sponsor asked the Agency to clarify what to evaluate for safety related to the device. FDA responded that in addition to items already broached in its written response to Question 4 (above), the sponsor should also perform accuracy testing after the device has been shipped, as well as shelf-life testing. FDA also asked the sponsor to include any observations/complaints by study subjects regarding device use.

Question 5: Mylan intends to conduct a summative human factors study in 120 users, using simulated use conditions in accordance with the Agency's advice provided in the Type C written response dated October 22, 2012 (Ref ID 3206476).

a. Does the Agency agree that the proposed summative human factors study design adequately supports approval of the NDA?

b. Mylan understands, from the scientific literature, that similar prefilled pens on the market are used by pediatric patients as well as adults. Mylan Insulin glargine injection is intended for administration in adults and children. Mylan will conduct the summative human factors study in adults (i.e. 18 years and above). Is this acceptable to the Agency as a basis of approval?

c. Mylan plans to conduct the proposed summative human factors study using one of its insulin analogues such that any differences in the IFU for device use with other insulin analogue candidates, such as the additional "mixing step" in insulin suspensions, are also validated. Since the summative human factors study for the prefilled pen is independent of the drug involved, is this approach acceptable to the Agency?

d. In the event that Mylan changes the color of the pen for aesthetic appeal alone, and makes no change to the functionality of the device, will the summative testing conducted with the current pen color still be acceptable for product approval?

FDA Response to Question 5:

a. The general approach employed in your Human Factors/usability validation study appears adequate to support your proposed 505(b)(2) application in collecting the necessary data to demonstrate safe and effective use. However, there are some issues. As noted above in our response to Question 1, we are unable to comment on whether the design of these studies, in conjunction with other data, would provide adequate data to support a determination of therapeutic equivalence.

- **We do not agree with your plan to have 50% of your participants use the insulin suspension in this study. All participants should use your proposed insulin glargine pen device for this study since the goal of this study is to demonstrated usability of your insulin glargine pen. We do not agree with**

your plan to validate your Instruction For Use (IFU) for other insulin suspensions that involve an additional "mixing step." A separate human factors validation study needs to be conducted with the required number of participants for that particular insulin. If you want to include your insulin suspension prefilled pen in this study, you will need to double the number of participants so that each group of participant who will use the each type of insulin pen (i.e. insulin glargine and insulin suspension) has at least 15 participants.

Group	User	Insulin Type	Trained	Untrained	Total
1	Injection Naïve	glargine	N = 15	N = 15	N = 60
		suspension	N = 15	N = 15	
2	Injection Experienced	glargine	N = 15	N = 15	N = 60
		suspension	N = 15	N = 15	
3	Lantus Pen Users	glargine	N = 15	N = 15	N = 60
		suspension	N = 15	N = 15	
4	HCPs	glargine	N = 15	N = 15	N = 60
		suspension	N = 15	N = 15	
	Total		N = 120	N = 120	N = 240

- **Additionally, you have not clearly described the use differences between the clear insulin and insulin suspension. We are unclear if the mixing step is the only difference, and what the mixing step entails in terms of different user interactions. Provide a comparison table that include all of the use steps for each insulin type and highlight the differences between the two IFUs. In addition, please describe the drug characteristics for the two insulin types, and clarify if those can impact user's ability to prepare and/or mix.**
- **We recommend conducting the pen identification task prior to the usability test of the device. Please provide a list of pens (insulin pens from other companies) and the rationale for inclusion in your pen identification task.**
- **Please refer to the comments provided in October 22, 2012, repeated here for your convenience: "Include a case-based protocol for differentiation between Biocon's pen and pens from other product lines likely to be prescribed with Biocon's pen, such as short- or rapid-acting insulin (e.g., insulin aspart, regular human insulin, etc.) as well as intermediate- and short-acting insulin combination products (e.g., NPH and regular human insulin combination or insulin aspart and insulin aspart protamine combination)."**
- **For the untrained group, we recommend that you do not specifically instruct participants to read the IFU prior to attempting to self inject. This will**

simulate the actual use scenario regarding what users will do when training is not provided.

b. Regarding pediatric users, your table 1.6.1 shows the different populations:

Age	Recommendation
6 years to 8 years	Administration by caregiver/ parent
8 years to 12 years	Self-administration or administration by caregiver/ parent (as determined by caregiver/ prescribing physician).
12 years to 18 years	Self-administration or administration under supervision of a caregiver/ parent.
18 years onwards	Self-administration*
**A patient's ability to self-administer will be assessed by the prescribing physician. Geriatric patients may require assistance/ may be unable to self- administer insulin and/or insulin analogues.*	

You stated that self-administration or administration by caregiver/patient will be determined by caregiver/prescribing physicians for pediatrics between the age of 8 and 18 years old. This type of rationale makes it possible that some of these pediatric users may self-administer, and if that is the case, we expect to see 15 participants that are representative of this user group in your study. Alternatively, we ask that you specify the requirement that "no self-administrations should be performed by pediatric users under the age of 18 years old" in your product labeling and training.

c. Refer to our response to Question 5a.

d. Please ensure that the pens that you will evaluate in the summative study represent the finalized commercial product (i.e. pen color, including label and labeling). We recommend that you evaluate the appearance prior to validation. Alternatively, perform another differentiation study to ensure that the color change does not impact the user's ability to differentiate the pen from other products.

Additional comments:

- **Include narrative and graphical description of your device, and describe the device user interface.**
- **Submit your human factors validation study protocol, finalized labeling including IFU, and analysis of use-related risks for review prior to implementation.**

Question 5 Discussion: **No additional discussion.**

Question 6: Mylan intends to follow the universal color code system initiated by the International Diabetes Federation (IDF), as a reminder aid so users can associate a color with its insulin formulation, where available. This is expected to reduce confusion and uncertainty between insulin and insulin analogues for users. If an IDF color is not available for a particular product, then the color will be similar to that used by the innovator, Sanofi.

Does the Agency agree with Mylan's approach to color-based differentiation between the same pen for different insulin analogues?

FDA Response to Question 6: **Your plan appears acceptable. However, we will need to review the labels and labeling for each product to ensure that the differentiation scheme of your insulin pens is acceptable in conjunction with the differentiation study results.**

Question 6 Discussion: **No additional discussion.**

2.4 Nonclinical

Question 7: Glycosylated forms of insulin glargine are product-related variants generated during the manufacture of Mylan Insulin glargine drug substance. Through extensive characterization, Mylan has identified and elucidated the structures of each of the 5 glycosylated impurities. Additionally, as part of the qualification strategy, each of the impurities has been studied in several in-vitro/functional assays. A three-way, comparative, 28-day, repeat-dose toxicity study in Wistar rats has been successfully completed.

a. Does the Agency concur that the results from the three-way, 28-day repeat-dose toxicity study in rats predict the safety of glycosylated variants present at low levels in Mylan Insulin glargine?

b. Does the Agency agree that no additional nonclinical studies would be required to support approval of Mylan Insulin glargine?

FDA Response to Question 7:

a. Based on your description provided in your briefing document, these impurities (glycosylated variants of drug substance; Basalog Batch G030008) appear to be addressed in your 3-way comparative 28-day bridging toxicity rat study (study No. G11066).

Please provide the level of these glycosylated variants in Lot BBS-0611003 used in the 90 day rat study (Study No. G4668) and 90 day rabbit study (Study No. G4669) as well as the 3-way comparative 28-day bridging rat toxicity study (study No. G11066). Please identify if the "Lantus" used in these 90-day toxicity studies is US-approved Lantus or EU-approved insulin glargine.

The adequacy of non-clinical studies will be determined during review of your NDA submission along with the CMC determination of adequacy of your impurities characterization. If there is any new concern identified by CMC, additional nonclinical studies may be required to assess these impurities and concerns.

b. See response to Question 7a and 8, as you may need a nonclinical study to bridge between proposed manufacturing sites.

Question 7 Discussion: **No additional discussion.**

2.5 Clinical

Question 8: Mylan plans to rely on the Agency's finding of safety and efficacy for the reference drug, Lantus (NDA 21081). Mylan plans to use Lantus sourced from the EU and Lantus sourced from US as comparators in the proposed clinical development program. A scientific bridge between Lantus sourced from the US, and Lantus sourced from the EU has been established.

Does the Agency agree that, the proposed three-way comparative development program and data generated to date for Mylan Insulin glargine, Lantus sourced from the US, and Lantus sourced from the EU is adequate to establish a scientific bridge?

FDA Response to Question 8: **As a preliminary matter, FDA notes that E.U.-approved Lantus is not an approved product in the United States. Accordingly, it is not a "listed drug" for which FDA has made a finding of safety and effectiveness.[1] The 505(b)(2) approval pathway may be used for a product that is demonstrated to be sufficiently similar to a listed drug (i.e., U.S.-approved Lantus) to permit reliance, where scientifically justified, on FDA's finding of safety and/or effectiveness for the listed drug to support the approval of a new drug application. See FDA's previous regulatory comments regarding the 505(b)(2) pathway.**

If Mylan seeks to use data from a clinical trial comparing Mylan insulin glargine to E.U.-approved insulin glargine to support a demonstration of sufficient similarity to the U.S.-approved listed drug and thereby justify reliance, in part, on FDA's finding of safety and effectiveness for the listed drug, Mylan should provide adequate data or information to scientifically justify the relevance of this comparative data to an assessment of similarity and establish an acceptable scientific bridge to the U.S.-approved listed drug. The type of bridging data needed to provide adequate scientific justification for this approach would include data from analytical studies (e.g., structural and functional data) that directly compare all three products (i.e., Mylan Insulin glargine, US-approved Lantus, and EU-approved insulin glargine) and bridging clinical PK and PD study data for all three products. All three pairwise comparisons should meet the pre-specified acceptance criteria for analytical and PK and PD similarity. The adequacy of this scientific justification and bridge to the U.S.-approved listed drug would be a review issue.

[1] We note that your submission uses the term "reference product." The term "reference product" means the single biological product licensed under section 351(a) of the PHS Act (see section 351(i)(4) and 351(k) of the PHS Act). There currently is no "reference product" licensed under section 351(a) of the PHS Act for a proposed insulin glargine product. Since you intend to use the 505(b)(2) approval pathway, in this response we use the term "listed drug" to refer to US-approved Lantus.

While a 3-way comparative bridging 28-day rat toxicity study has been performed with both US-approved Lantus and EU-approved insulin glargine, the levels of impurities have not been provided (See response to Question 7a).

You plan to utilize two manufacturing sites for your proposed product and demonstrate comparability of products from these sites using primarily analytic/chemical means. This type of CMC data is required for the NDA filing. If you plan to utilize products from both sites in your Phase 3 clinical program, then adequate safety data will be needed to show comparability of safety prior to clinical use. Therefore additional nonclinical safety data (e.g. subchronic toxicity) will likely be needed (See response to Question 7A).

See the response to Question 3 c regarding the chemistry requirements.

Based on the results reported in the briefing book, it appears that a clinical PK and PD bridge has been established between US-approved Lantus and EU-approved insulin glargine. However, the determination of the adequacy of clinical PK and PD bridge will be a review issue.

Question 8 Discussion: **The sponsor clarified that it plans to use EU-approved insulin glargine as an active control in its Phase 3 study for type 1 diabetes mellitus and US-approved Lantus as an active control in its Phase 3 study for type 2 diabetes mellitus. FDA acknowledged the clarification, and recommended that a single product (i.e., EU-approved insulin glargine or US-approved Lantus) be used as an active control, rather than using two distinct products (i.e., EU-approved insulin glargine and US-approved Lantus) in a single clinical study.**

FDA clarified the use of two different methods (Mercodia and Dako) for sample analysis from bioequivalence studies. Sponsor stated that backup samples from Study GLARGCT100111 were reanalyzed using a more sensitive assay following FDA advice from previous interactions.

Post-Meeting FDA Comment to Question 8: In your submission, in addition to reporting the serum M2 values from the new assay, also report the C-Peptide values at baseline and for the duration of clamp. Also include the relevant bioanalytical method reports for insulin, C-peptide, and glucose analytes.

Question 9: Mylan plans to conduct two supportive clinical studies. Mylan intends to conduct a 52-week comparative study in T1DM patients with approximately 400 patients using EU sourced reference product. The planned T1DM study will have a 6-week run-in period followed by a 52-week treatment period and finally an additional 4-week of follow-up. In addition, Mylan intends to conduct a 24-week comparative clinical study to evaluate safety, immunogenicity, and efficacy in T2DM patients with at least 500 patients using EU sourced reference product. The T2DM study will have a 6-week run-in period followed by a 24-week treatment period and a 4 week follow-up.

a. Does the Agency agree that the proposed T1DM and T2DM studies have the appropriate design, sample size and endpoints to support approval?
b. Given that Mylan will provide a scientific bridge between the Lantus US and Lantus EU, does the Agency agree that the use of Lantus sourced from the EU in the proposed T1DM and T2DM studies has no impact on its role in supporting a TE determination?
c. Does the Agency agree with Mylan's plan to include 6 month data from the T1DM study for the initial NDA submission and to submit the 12 month data as an amendment to the NDA or as a post approval commitment?

FDA Response to Question 9:

a. See our response to Question 1. Based on the synopsis provided in your briefing document, we have the following preliminary comments for the proposed T1DM (MYL-GAI-3001) and T2DM (MYL-GAI-3002) studies. We strongly recommend that you submit the full study protocols along with any statistical analysis plan for our review and await our comments before commencing your Phase 3 studies. The protocol should also include how you will evaluate safety related to device.

- **Your proposed sample size of 200 patients per arm for Study MYL-GAI-3001 is insufficient to assess important safety events. Increase the sample size per treatment arm to at least 250 subjects to ensure that there will be a sufficient safety database.**

- **Clarify the sample size for Study MYL-GAI-3002. The synopsis stated 560 subjects, whereas the main body of the briefing document stated 500 subjects will participate in this study.**

- **We note that T2DM patients already on Lantus are eligible for enrollment in Study MYL-GAI-3002. In order to facilitate detection of anti-insulin antibodies and their titers in the two treatment arms, we also recommend that you enroll T2DM subjects who are naïve of insulin treatment for participation in the study. The randomization can be stratified by prior insulin use (yes or no) and you should analyze antibody response separately for insulin-naïve and non-insulin-naïve subjects.**

- **We note that in the HbA1c inclusion criterion is <8.5% for Study MYL-GAI-3002. To ensure that there will be opportunity to sufficiently titrate insulins and more convincingly show non-inferiority, you should enroll patients with sufficiently high baseline HbA1c (e.g., mean baseline HbA1c ~8.5%).**

- **We agree with the non-inferiority margin proposed. However, iInsulin is a product that is titrated to achieve a targeted glycemic effect. Therefore, the risk/benefit profile for your insulin glargine (compared to Lantus) will also be based on other important effects, such as rates of hypoglycemia, changes in body weight, and other safety issues that emerge during the NDA review.**

- **Adequate titration of insulins will be a critical factor in determining a meaningful improvement in HbA1c over the duration of the study and the interpretability of study results. Therefore, we recommend strategies to ensure that appropriate titration of insulin doses occur, such as a titration algorithm, and/or review of glucose data while the trials are ongoing with feedback to investigators when there is evidence of inadequate titration. You should consider a titration algorithm that takes into account fasting plasma glucose level so that most titration occurs by Weeks 6-12. If insulin doses are not relatively stable after Week 12, interpretation of study results could be affected because HbA1c at Week 24 will not accurately reflect glycemic control.**

- **We ask that you clarify which are key secondary endpoints and how you will control for Type 1 error in the study protocol.**

- **You propose 'rate of hypoglycemic events per 30 days at 4 weeks and 24 weeks' as one of secondary endpoints. Evaluation of hypoglycemia should be based on the entire treatment intervention phase (i.e., titration and maintenance phase). Titration and maintenance phases provide relevant clinical information that should be captured in the analysis.**

- **Your trial is open-label and reporting bias is possible for episodes of hypoglycemia that rely on fingerstick glucose measurements alone without clinical symptoms.**

- **The dropout rate, 2%, for Study MYL-GAI-3002 seems low and unrealistic. You may want to adjust sample size with a higher anticipated dropout rate.**

b. Your question regarding the acceptability of use of EU-approved insulin glargine in clinical studies intended to support a demonstration of therapeutic equivalence of Mylan insulin glargine to U.S.-approved Lantus requires further internal Agency discussion and we are unable to provide a response at this time.

c. We recommend that your NDA should be complete at the time of submission, as the 12 month data from this study are important in determining the safety of your drug in this population.

Question 9 Discussion: **The sponsor asked the Agency to clarify what to evaluate for safety related to the device. FDA provided the following clarification: The overall safety profile for the combination product includes the device constituent; Examples of device related adverse events and device malfunctions include, but are not limited to, local skin reactions, wet injections, needle breakage, failure to inject, etc. FDA stated that it would be useful to provide details on the method / patient collection tool to capture details on the device related events in the protocol. The Agency can provide additional comments during protocol review.**

The sponsor stated that the key secondary endpoints are safety-related and do not plan to control for Type 1 error. FDA agreed that control for Type 1 error is not necessary for safety-related key secondary endpoints, but will be needed for any efficacy-related key secondary endpoints.

The sponsor provided information on titration guidelines for its Phase 3 studies. FDA reiterated that adequate titration of insulins will be a critical factor during the review process and recommended having a titration committee to review glucose data while the trials are ongoing to make sure that there is adequate insulin titration, and the sponsor stated that they will take that into consideration.

The sponsor clarified that the sample size for Study MYL-GAI-3002 is 560 subjects (not 500 subjects). The sponsor will enroll insulin-naïve subjects in their T2DM study as suggested by the Agency, but did not have a specific ratio for enrollment of insulin naïve subjects. FDA stated that there should be a ratio to make sure that sufficient number of insulin-naïve subjects are enrolled into the study, and will recommend a ratio to the sponsor after the meeting.

Mylan asked whether the use of EU-approved insulin glargine as an active control in a clinical study intended to support a demonstration of therapeutic equivalence of Mylan insulin glargine to U.S.-approved Lantus would pose an additional hurdle if they provided adequate bridging data. FDA reiterated that Mylan's question requires further internal Agency discussion and they were unable to provide a response at this time, but noted that this would be an additional factor to consider. FDA noted that if Mylan was proposing a clinical study to support a demonstration of therapeutic equivalence, the sponsor could submit a proposal for such a study with rationale for their study objectives and design, and the Agency may review their proposal and provide comments.

Post-Meeting FDA Comment to Question 9: We recommend that 40-60% of total subjects enrolled in Study MYL-GAI-3002 are T2DM subjects who are naïve of insulin treatment.

Question 10: Mylan plans to execute the T1DM and T2DM clinical studies using prefilled pens. No additional studies are planned using vials. The formulation for all presentations of Mylan

Insulin glargine is the same. We anticipate that the T1DM and T2DM studies done with the prefilled pen will be sufficient for the approval of the vial also.

Does the Agency agree that no further clinical studies are required using vials to support approval of the vial presentation?

FDA Response to Question 10: **We agree that additional clinical studies using vials are not necessary for approval of the vial presentation if the clinical properties of your insulin glargine are expected to be the same for all presentations. Refer to comments from other FDA disciplines (Pharmacology/Toxicology, CMC, and Clinical Pharmacology) on the other aspects of your proposal.**

Question 10 Discussion: **No additional discussion. Mylan withdrew their new question on slide 20.**

Post-Meeting FDA Comments to Question 10: Our previous response is contingent upon studies on leachables and extractables from the vials. If these studies show that the impurities from the vials are different from the prefilled pens, you may need additional data or clinical studies (e.g., immunogenicity data) to support approval of the vial presentation.

Question 11: Patients recruited for T1DM study will have at least 3 months history of exposure to a stable dose of Lantus. The pre-exposure to Lantus is intended to reduce differences in baseline immunogenicity between the two treatment arms. We will be collecting blood samples for the immunogenicity assessment at screening, baseline, and weeks 12, 24, 36 and 52. We are planning on conducting an interim analysis after the patients complete 24 weeks of treatment and submit the clinical study report to Europe for marketing authorization approval. Thus the immunogenicity analysis will be conducted at 2 time points during this 52-week study at 24 weeks and at 52 weeks.

a. Is the proposed immunogenicity sampling at screening, baseline, and weeks 12, 24, 36 and 52 acceptable?

b. Mylan is planning to conduct immunogenicity analysis for all the patients at 2 time points; an interim analysis at 24 weeks and a final analysis at 52 weeks. Is the proposed analysis plan acceptable?

FDA Response to Question 11: **See our response to Question 9c. We recommend that you submit the final analysis with 52 weeks data at the time of NDA submission.**

The proposed immunogenicity sampling is acceptable to support your proposed 505(b)(2) application . The immunogenicity analysis should include the effect of treatment on anti-insulin antibody development, and also correlate these antibodies with glycemic response (i.e., HbA1c), hypoglycemia, allergic reactions, and emerging safety issues. As noted above in our response to Question 1, we are unable to comment

on whether the design of these studies, in conjunction with other data, would provide adequate data to support a determination of therapeutic equivalence.

Question 11 Discussion: **The sponsor asked whether 9 month data from the T1DM study is sufficient for NDA filing, with the full 12 month data to be submitted during regulatory review. FDA recommended that the sponsor file the NDA with 12 month data from its T1DM study.**

FDA stated that interim data analysis should be included in their statistical analysis plan.

Post-Meeting FDA Comments to Question 11a: We also ask that you obtain samples for immunogenicity analysis at 10-15 days and 28-35 days after randomization.

Question 12: The presentations of the test product and the comparator planned to be used for clinical studies are clearly distinguishable (different prefilled pens). We are unable to double mask the studies and the double dummy design technique is not ethical or feasible, therefore, the proposed studies will be open label. However, we plan to conduct the efficacy parameter (HbA1C) and safety parameters (Biochemical laboratory tests) in a blinded manner. This approach diminishes potential bias that would otherwise exist from an open-label, trial design as these are objective parameters.

Does the Agency agree with the open label design for the proposed clinical studies?

FDA Response to Question 12: **The open label design is acceptable given that you are using prefilled pens in these clinical studies.**

Question 12 Discussion: **No additional discussion.**

Question 13: Mylan plans to perform the clinical trials with Lantus and Mylan Insulin glargine using prefilled pens. EU guidance requires that the retained samples be stored in the EU. FDA guidance does not explicitly state where the testing samples should be stored. Mylan plans to store samples, equivalent to two times the amount needed for full analytical testing from all batches used in the clinical trials of test and reference product, in the EU.

Does the Agency agree with Mylan's proposal to store two times the amount needed for full analytical testing of batches used in clinical trials (both test and reference product) in the EU?

FDA Response to Question 13: **Yes, we agree that the reserved sample should be at least twice the quantity necessary for all analytical testing.**

Question 13 Discussion: **No additional discussion.**

Question 14: Mylan is plans to execute a clinical study in T1DM patients. T1DM patients are typically treated with Insulin/Insulin Analogs per standard of care. It is practically impossible to

obtain serum from insulin treatment naïve T1DM patients. In addition our T1DM study is designed to only include patients that have at least a 3-months history of exposure to a stable dose of Lantus. For these reasons Mylan would like to propose to use pre-dose sera from the T1DM study patients to establish cut-points using the balanced design.

Does the Agency agree with Mylan's approach to use pre-dose patient sera to establish screening and confirmatory cut-points during immunogenicity method validation?

FDA Response to Question 14: **Response to Question 14 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

Question 14 Discussion: **Yes, in this population this is acceptable provided samples that are confirmed to have anti-drug antibodies are not used for the determination of the assay cut point.**

Post-Meeting FDA Comments to Question 14: See Discussion above; no additional post-meeting comments.

Question 15: The T1DM study has been designed to compare the immune responses between Mylan Insulin glargine and Lantus. Any differences in immune responses between the treatment arms could be assessed with the currently planned analytical methods. The additional analysis of anti-drug antibody (ADA) positive samples for cross-reactivity to insulin or related analogues would have no impact on the outcome of the trial. In case the characterization of cross-reacting ADA is required Mylan plans an additional Comprehensive Confirmatory Analysis phase where the confirmed positive samples undergo pre-incubation with an excess unlabeled human insulin and insulin lispro prior to adding Lantus or Mylan Insulin glargine. The difference in percent inhibition between Mylan Insulin glargine and Lantus will be determined.

a. Does the Agency agree that an analysis of anti-drug antibody positive samples for cross-reactivity to insulin or related analogues is not required for the immunogenicity assessment of the clinical studies?

b. In case the analysis of cross-reacting ADA is required does the Agency agree with Mylan's approach of using excess unlabelled human insulin and insulin lispro to analyse confirmed positive samples?

FDA Response to Question 15: **Response to Question 15a and 15b will be provided in the final Meeting Minutes as Post-Meeting Comments.**

Question 15 Discussion: **No, the Agency does not agree that an analysis of anti-drug antibody positive samples for crossreactivity is unnecessary. In general, the approach of adding excess unlabeled human insulin to assess crossreactivity is adequate, but a final determination will be made upon review of the assay.**

Post-Meeting FDA Comments to Question 15: See Discussion above; no additional post-meeting comments.

Question 16: During method development, Mylan plans to compare the Radio Immuno-precipitation and the Meso-scale Discovery assay format in terms of method validation parameters including intra and inter assay precision for screening, confirmatory and titration assays, sensitivity, selectivity, specificity and free drug tolerance. Based on the data obtained from the comparison, Mylan intends to select one assay format for validation and sample analysis.

Does the Agency agree with Mylan's approach of comparing both radioactive and non-radioactive assay formats, and selecting a single format for validation and sample analysis?

FDA Response to Question 16: **Response to Question 16 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

Question 16 Discussion: **The Agency has no preference for assay format. The Sponsor will need to select an assay format and validate its performance prior to testing the samples of the pivotal trials. A final determination will be made upon review of the SOP and validation of the assay used.**

Post-Meeting FDA Comments to Question 16: See Discussion above; no additional post-meeting comments.

Question 17: Mylan is planning to use two separate immunogenicity assays using an identical analytical platform (RIPA or MSD), one for Mylan Insulin glargine and one for Lantus. A blinded anti-drug antibody analysis would require all samples being analyzed in both assays resulting in two data sets for each sample. Mylan intends to un-blind the study samples at the CRO before initiation of sample analysis.

Does the Agency agree with Mylan's approach of un-blinding the immuno-genicity samples before initiation of the sample analysis?

FDA Response to Question 17: **Response to Question 17 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

Question 17 Discussion: **The advantages of having a single platform for testing the samples for antibodies to Mylan and Lantus product were discussed. The Agency does not agree that unblinding the samples is necessary prior to testing them. The sponsor requested that additional discussion be held regarding this topic between the Sponsor and the Agency.**

Post-Meeting FDA Comments to Question 17: See Discussion above; no additional post-meeting comments.

Question 18: Does the Agency agree with Mylan's approach of using a competitive ligand binding Assay format for the evaluation of neutralizing antibodies?

FDA Response to Question 18: **Response to Question 18 will be provided in the final Meeting Minutes as Post-Meeting Comments.**

Question 18 Discussion: **This question was not discussed during the meeting but the Sponsor requested a comment.**

Post-Meeting FDA Comments to Question 18: The approaches described to assess neutralizing activity of samples that test positive for antibodies to the product is adequate, but a final determination will be made upon review of the SOP and validation of the assay.

Additional FDA Comment:
FDA recommends that you submit your proposed proprietary name for this product for review. (See the Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

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/s/

JEAN-MARC P GUETTIER
04/04/2014

EXHIBIT C

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210605

REFUSAL TO FILE

Mylan GmbH
Attention: Suzanne Kiani
Senior Director, Regulatory Science, Biologics
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Kiani:

Please refer to your New Drug Application (NDA) dated and received April 27, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin glargine injection 100 units/mL.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

The NDA is incomplete because it does not on its face contain information required under section 505(b) of the FDCA and 21 CFR 314.50 (see 21 CFR 314.101(d)(3)).

Specifically, you have submitted a 505(b)(2) application for the proposed to-be marketed insulin glargine product manufactured using Process VI at a facility in Malaysia (i.e., Process VI product), while the insulin glargine product studied in the Phase 3 clinical trials was manufactured using Process V at a different facility in India (i.e., Process V product). We consider the manufacturing change to be a major change.

Based on the specific manufacturing changes made, additional clinical safety and efficacy bridging data, including an assessment of immunogenicity, are needed to establish that the efficacy and safety data generated with Process V product (i.e., Phase 3 product) is relevant to Process VI product and can be used to support a determination that the proposed to-be marketed product (i.e., Process VI product) is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus.

In Study MYL-1501D-1001, only $AUC_{0\text{-}24h}$, a pharmacokinetic endpoint, was used as the primary endpoint and pharmacodynamic (PD) endpoints were considered secondary. PD endpoints, such as $AUC_{GIR0\text{-}24h}$, are important endpoints when comparing across insulin glargine products, and are generally used as additional primary endpoints in comparisons. In Study MYL-1501D-1001, PD similarity was not demonstrated for $AUC_{GIR0\text{-}24h}$, $AUC_{GIR0\text{-}12h}$, and

$AUC_{GIR12-24h}$ between Process V product (i.e., Phase 3 product), and Lantus. Differences in PD endpoints were also noted across other comparisons ($AUC_{GIR0-12h}$, and $AUC_{GIR12-24h}$) between Process V and VI products.

While the following are not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

Biostatistics

1. The submission did not include subgroup analyses of safety and effectiveness by gender, age, and race that are required by FDA regulations (21 CFR 314.50).

Drug Substance

2. To be consistent with the USP Monograph for Insulin Glargine which includes meeting the requirements for Insulin Assay, Bioidentity Test <121>, revise the MYL-1501D drug substance specifications to include this test. We do not agree that an RP-HPLC assay can be substituted for a bioassay as part of the specifications for the MYL- 1501D drug substance. We remind you that in the April 4, 2014, End-of-Phase 2 Meeting Minutes for IND 105279 for your insulin glargine injection product, the Agency recommended to, "Add a bioassay to the drug substance specification, and provide data to support the correlation of 0.0364 mg of insulin glargine being equal to 1 Unit of insulin glargine," (p. 5). Further, during this meeting, the Sponsor discussed that "A bioassay based on USP <121> will be included in the drug substance specification," (p. 6).

3. A USP Insulin Glargine Reference Standard is available and should be used going forward as a reference standard for the MYL-1501D drug substance and drug product. In support of the change to the USP standard, provide data comparing the USP Insulin Glargine Reference Standard and the Insulin Glargine EPCRS (European Pharmacopoeia Chemical Reference Substance) that is currently used to qualify the working standards.

Drug Product

4. Regarding your drug product specification, we have the following comments.
   a. Provide an assessment of how your test methods and acceptance criteria proposed for drug product comply with the USP insulin glargine injection monograph.
   b. For those methods which are not aligned with the USP insulin glargine injection monograph, provide data to support the equivalency of your analytical methods to those in the USP insulin glargine injection monograph. Refer to comment #4 (Drug Substance).
   c. We note that your RPUPLC potency assay uses a single standard to calculate the potency of an unknown sample, whereas the USP monograph for Insulin Glargine Injection requires the construction of a calibration curve based on three standards used for the test. Justify your choice of the single standard.

d. Revise your specification to include an acceptance criterion for the color and clarity of the drug product solution packaged in vials and cartridges. Include appropriate reference standard for testing (e.g., Ph. Eur. 2.2.1 and 2.2.2).

e. Insulin glargine content in the drug product should be specified in mg/mL as well as in Units /mL.

5. The expiration dating period and in-use shelf life for the product will be based on real-time stability data and in-use stability data for the combination product.

6. Provide information on the apparent weight-average molecular weights and hydrodynamic radii of insulin glargine in your drug product in comparison to Lantus based on Static or dynamic light scattering studies.

7. Provide the projected environmental assessment (EA) calculation information for the expected levels of your product introduced into the aquatic environment.

Drug Process:

8. Please submit the Executed Batch Manufacturing Record of the drug product lots manufactured at Bangalore, India, which were used in the Phase 3 clinical studies (study number MYL-GAI-3001, MYL-GAI-3002).

9. Since the stability of this drug product is temperature dependent, please provide the following information:
   a. Define the manufacturing environmental condition.
   b. Define the time limit for exposure of product to ambient temperature (below 30°C) during manufacturing operation and justify your proposed limit.
   c. Define the hold time and storage condition for process intermediates and the total processing time during the drug product manufacturing process, and provide justification.
   d. Update Module 3.2.P.3.4 with the information requested above.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting (see 21 CFR 314.101(a)(3)).

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you

requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.

If you have any questions, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely yours,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Reference ID: 4624497

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/s/

JEAN-MARC P GUETTIER
06/26/2017

EXHIBIT D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210605

COMPLETE RESPONSE

Mylan GmbH
Attention: Suzanne Kiani
Senior Director, Regulatory Science, Biologics
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Kiani:

Please refer to your New Drug Application (NDA) dated and received April 27, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for insulin glargine injection 100 units/mL.

We also acknowledge receipt of your amendment dated May 11, 2018, pertaining to antimicrobial effectiveness testing, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL-RELATED MAJOR DEFICIENCIES

1. Your 505(b)(2) application requests approval of your proposed insulin glargine product manufactured using Process VI at a facility in Malaysia (i.e., Process VI product), while the proposed insulin glargine product studied in the phase 3 clinical trials was manufactured using Process V at a different facility in India (i.e., Process V product). We consider the manufacturing change to be a major change.

   Based on the specific manufacturing changes made, additional clinical safety and efficacy bridging data, including an assessment of immunogenicity, are needed to establish that the efficacy and safety data generated with Process V product (i.e., phase 3 product) is relevant to Process VI product and can be used to support a determination that the proposed to-be-marketed product (i.e., Process VI product) is sufficiently similar to Lantus to justify reliance, in part, on FDA's finding of safety and effectiveness for Lantus.

2. You have not submitted the bridging data necessary for approval of the vial presentation of your proposed product. The recommendation regarding the need for PK/PD data between your cartridge and vial presentations was also conveyed during the Type A, Informal Conference held on August 15, 2017. Submit the results from the proposed study (Study MYL-1501D-1004) to address this deficiency.

PRODUCT QUALITY-RELATED MAJOR DEFICIENCIES

3. During a recent inspection of Biocon Sdn. Bhd. FEI#3011248248, a manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

4. CMC microbiology review noted the following deficiencies:

   i. Lack of method suitability data for endotoxin, sterility, and antimicrobial effectiveness testing (AET).

   ii. Lack of AET data supporting the product expiry from stability.

   To resolve these deficiencies, provide the following in your resubmission.

   a) Provide AET results for the 10 mL drug product presentation, which contains polysorbate 20, (b) (4) at or below the minimum content specification for release or stability testing (whichever is lower). Also, provide a commitment to conduct antimicrobial effectiveness testing according to USP <51> or equivalent methodology on at least one primary stability batch per drug product presentation (i.e. one 3 mL cartridge drug product presentation and one 10 mL vial drug product presentation) at the end of the proposed shelf life. Refer to ICH Q1A Stability Testing of New Drug Substances and Products for new drug products.

   b) It is stated in your March 19, 2018 response that bacterial endotoxins testing method suitability was performed for the 10 mL drug product presentation including polysorbate 20 and the 3 mL cartridge drug product presentation. However, only brief summaries were provided. Provide the reports showing the actual results for the bacterial endotoxins method suitability studies.

      It is stated in your March 19, 2018 response that sterility testing method suitability was performed for the 10 mL drug product presentation including polysorbate 20 and the 3 mL cartridge drug product presentation. However, only brief summaries were provided. Provide the reports showing the actual results for the sterility method suitability studies.

HUMAN FACTORS-RELATED MAJOR DEFICIENCIES

5. Our review determined that there were an insufficient number of untrained injection naïve pediatric patients in each user group of the human factors validation study. Our review of the Instructions for Use (IFU) identified several areas that should be modified from a medication error perspective (see **INSTRUCTIONS FOR USE** below). You may also consider additional labeling changes as necessary. Once you finalize your proposed to-be-marketed IFU, you should conduct an additional human factors validation study with 15 untrained injection naive pediatric patients.

6. We note that the results of product differentiation showed multiple study participants failed to select the Semglee pen. Our review of the proposed carton and container labeling (see **CARTON AND CONTAINER LABELING** below) identified multiple areas that should be modified to enhance product differentiation. Therefore, you should implement these modifications, in addition to any other labeling changes that you consider to be necessary, finalize your proposed to-be-marketed carton and container labeling, and conduct a differentiation study with all the intended user populations for the product with at least 15 users in each distinct user group.

   We recommend that you submit the protocols for the usability study and differentiation study for Agency review and feedback prior to starting your studies.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products;
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential;
- Regulations and related guidance documents;
- A sample tool illustrating the format for Highlights and Contents;
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances;
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our review of your submitted proposed labeling, we identified the following labeling issues that should be addressed in your resubmission:

1. Dosage and Administration: Section 2.1 Important Administration Instructions

   a. We recommend replacing the word [redacted] (b) (4) in the statement "administer Semglee subcutaneously into the abdominal area, thigh, or [redacted] (b) (4) …" to "upper arm" as this corresponds to the instructions provided in the Instructions for Use (IFU). In addition, we recommend adding "buttocks" as an administration site to align with the information provided in the IFU.

   b. We recommend adding the statement "Use the Semglee prefilled pen with caution in patients with visual impairment." as the final bullet in this section.

2. Dosage and Administration: Section 2.2 General Dosing Instructions

   a. We recommend adding the statement "Semglee prefilled pens are designed to dial doses in 1 unit increments" as the final bullet in this section.

3. Dosage and Administration: Section 2.4 Changing to Semglee from Other Insulin Therapies

   a. We do not agree with removing the statement [redacted] (b) (4) [redacted] (b) (4). Therefore, we recommend adding the following statement as a new bullet this section: "In patients changing from once daily NPH insulin to once daily dose of Semglee, the recommended initial Semglee dose is the same as the dose of NPH that is being discontinued."

4. How Supplied/Storage and Handling: Section 16.1 How Supplied
   a. We recommend reformatting this section using the following table to present this information.

Semglee	Total Volume	Concentration	Total Units Available in Presentation	Dose Increment	NDC Number	Package Size
U-100 vial	10 mL	100 units/mL	1,000 units	n/a	[redacted] (b) (4)	1 vial
U-100 prefilled pen	3 mL	100 units/mL	300 units	1 unit		1 pen
						3 pens
						5 pens

5. How Supplied/Storage and Handling: Section 16.2 Storage
   a. We recommend revising the temperature presentations in the table to present the Fahrenheit temperatures before the Celsius temperatures as this coincides with the temperature presentation in the IFU. In addition, Fahrenheit temperature is more likely to be understood by end users in the US.

Prior to resubmitting the proposed labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

We reserve additional comments on the proposed labeling until the application is otherwise adequate.

INSTRUCTIONS FOR USE

Submit draft Instructions for Use (IFU)-Pen labeling revised as follows:

1. We recommend that you revise the statement (b) (4) (b) (4) (b) (4) to read as follows for improved clarity: "Semglee is a prefilled disposable pen injector that contains a total of 300 units of insulin glargine. One pen contains multiple doses of medicine. You can select doses from 1 to 80 units in steps of 1 unit." In addition, we recommend adding the statement "If your prescribed dose is more than 80 units, you will need to give yourself more than 1 injection." to this paragraph.

2. We recommend that you move the statement "**Do not** leave the needle attached to the Pen during storage or reuse needles." so that it is immediately following the statement "Always store the Pen with the cap on, to prevent contamination.": "Always store the Pen with the cap on, to prevent contamination. **Do not** leave the needle attached to the Pen during storage or reuse needles."

3. Due to the use errors involving the storage of Semglee observed in the HF study, we provide the following recommendations for the storage information. Under the Storage heading, we recommend adding section subheadings and bullet points to increase clarity and readability of the statements. In addition, we recommend modifications to the language as follows:

   Storage
   Unused Pens
   - Before using the Pen, store the cartons containing the Pen in the refrigerator between 36°F to 46°F (2°C to 8°C).
   - Unused Pens may be used until the expiration date printed on the carton, if

the Pen has been kept in the refrigerator.
- Do not freeze the Pen.

In-use Pen

- Before first use, take a Pen out of the refrigerator, rest it on a flat surface, and wait for it to reach room temperature between 59°F to 86°F (15°C to 30°C).
- While using the Pen, store it at room temperature up to 86°F (30°C). Do not put the Pen back in the refrigerator after using it.
- Always store the Pen with the cap on, to prevent contamination. Do not leave the needle attached to the Pen during storage or reuse needles.
- The Pen that you are using should be thrown away 28 days after the first use, even if the Pen has insulin left in it. See disposal instructions in Step 8.

Keep your Pen and needles out of sight and reach of children.

Always use a new sterile needle for each injection as this helps stop blocked needles and prevents infections.

4. Step 4: Select your dose
   a. We recommend the addition of the following as bullet points under this heading: "-The Pen dials 1 unit at a time.", "-The Dose Knob clicks as you turn it.", "-**Do not** dial your dose by counting the clicks because you may dial the wrong dose.", "-The **even** numbers are printed on the dial. The odd numbers are shown as lines."

   b. We recommend the addition of an image of an odd dose dialed on the device pen to correspond with the language added to indicate that odd doses are shown as lines in the dose window.

   c. We recommend that you add the statement "If you need a dose greater than 80 units, you should give it as two or more injections." so that it immediately follows the statement "**Do not** force the dose knob to turn beyond 80 units.": "**Do not** force the dose knob to turn beyond 80 units. If you need a dose greater than 80 units, you should give it as two or more injections." In addition, we recommend that these statements are moved to immediately follow the statement "The dose can be corrected by turning the dose knob in either direction until the correct dose lines up with the yellow dose pointer." to increase prominence of this information in the IFU.

5. Step 5: Select and clean the injection site
   We recommend revising the statement "Select the injection site as explained..." to read as follows:
   "Select the injection site as explained to you by your healthcare provider. Semglee is injected under the skin (subcutaneously) of your arms, hips, thighs, buttocks, or

abdomen. You should change your injection site for each injection. Clean with a new alcohol wipe and let your skin dry before you inject your dose."

6. Due to the use errors with holding the dose button down to complete the injection observed in the HF study, we provide the following recommendation for Step 6: Inject your dose:

   Under step D, revise the statement "hold the purple injection button...is injected." as follows for improved clarity: "after the dose window shows "0", continue to hold the purple injection button down and slowly count to 10 to make sure that the full dose of insulin is injected."

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling revised as follows:

A. Container Label-Pen

1. The proposed proprietary name, "Semglee," the established name, and the product strength lack prominence on the container label and are not readable. Thus, we request that you revise the label to remove the (b) (4) (b) (4) interfering with the readability of this information on the label in accordance with 21 CFR 201.10 (a) and 21 CFR 201.15 (a)(6). Consider presenting this text (proprietary name, established name, and product strength) on a white background with black letters in larger font to improve readability.

2. To improve readability of the proprietary name, we recommend increasing the font size of "Semglee" on the label.

3. To improve readability of the product NDC, we recommend using black font on a white background.

4. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.

5. Increase the font of the "For Single Patient Use Only" statement to improve readability of this information.

B. Container Label-Vial

6. The product strength, 100 units/mL (U-100), is illegible and difficult to read due to the use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability.

7. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.

C. Carton Labeling-Pen

8. The product strength, 100 units/mL (U-100), is illegible and difficult to read on each of the carton presentations due to your use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability. In addition, move the product strength statement so that it is directly below the proprietary name and established name on the principle display panel.

9. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.

10. We recommend that you consider moving the statement (b) (4) (b) (4) from the PDP so that it is immediately above (b) (4) on the back panel. In addition, for improved clarity of the statement, we recommend that you modify the statement to read "Use each pen within 28 days after initial use."

D. Carton Labeling-Vial

11. The product strength is illegible and difficult to read on each of the carton presentations due to your use of the (b) (4). We recommend that you consider placing this text on a white background with black letters in larger font for improved readability.

12. To improve the readability of the "Rx only" statement, we recommend removing the (b) (4) and using black font.

13. To improve readability of the carton contents, we recommend moving the statement "One 10 mL vial" above the blue box area and changing "one" to black font.

PROPRIETARY NAME

Please refer to correspondence dated, November 14, 2017, which addresses the proposed proprietary name, Semglee. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
   - Present tabulations of the new safety data combined with the original application data.
   - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
   - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

PRODUCT QUALITY

1) Revise the methods used for the determination of high molecular weight proteins (HMWP) and Product related substances to include the following:
    i. Equations used for impurity calculations to the HPLC and SEC impurity methods.
    ii. HPLC peak resolution criteria of not less than 2.0 for impurities to the system suitability

2) Provide the following additional information for aged drug product:
    i. Individual impurity profile comparison for MYL-1501 D drug product at the end of expiration (24 (b) (4) months) and in-use period using USP and in-house insulin glargine methods.
    ii. Individual impurity profile comparison for MYL1501 D drug product (cartridges and vial) with the available stability data of Lantus at T24 and T36 month time points using in-house impurity method.
    iii. Side by side accelerated stability impurity profile information for age matched Lantus and MYL-1501D vial and cartridge batches.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Michael G. White, Ph.D., Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

William Chong, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
05/17/2018

EXHIBIT E

FDA U.S. FOOD & DRUG ADMINISTRATION

NDA 210605

COMPLETE RESPONSE

Mylan GmbH
Attention: Suzanne Kiani
Senior Director, Regulatory Science, Biologics
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Ms. Kiani:

Please refer to your new drug application (NDA) dated and received April 27, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for insulin glargine injection 100 units/mL.

We acknowledge receipt of your amendment dated February 28, 2019, which constituted a complete response to our May 17, 2018, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS MAJOR DEFICIENCIES

During a recent inspection of Biocon Sdn. Bhd. FEI#3011248248, a manufacturing facility for this NDA, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the observations is required before this NDA may be approved.

We note that this is the second Complete Response letter for this NDA that has identified inspectional observations at this manufacturing facility as a deficiency. We recommend that you work with this manufacturing facility for your insulin glargine product and apply the necessary resources to address these inspectional observations in a timely manner.

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR

Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our review of your submitted labeling, we identified the following labeling issues that should be addressed in your resubmission:

In the Instructions for Use (IFU) labeling for the pen injector presentations submitted on August 28, 2019, you added the word "Needle" to the Step 8 title as follows "Step 8 Needle disposal." Please update the language in other places of the IFU that reference step 8. For example, the required supplies section states (b) (4) at the end of these Instructions for Use". Please revise to "See Step 8 Needle disposal" in all such instances where it is appropriate to do so.

In addition, the pen IFUs use (b) (4) to indicate sub-bullets under each step (i.e., Step 1, Step 2, etc.). Please note that we consider this to be a major change to the IFU, which was validated by the Human Factors study. Therefore, please revert to the prior sub-bullet letter designations (A, B, C, etc.) under each numbered step that were used in the Human Factors study.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling that is identical to the carton and container labels submitted on August 28, 2019.

PROPRIETARY NAME

Please refer to correspondence dated May 1, 2019, which addresses the proposed proprietary name, Semglee. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

(1) Describe in detail any significant changes or findings in the safety profile.

(2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
- Present tabulations of the new safety data combined with the original application data.
- Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

(3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

(4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

(5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

(6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

(7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.

(8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. Furthermore, as explained in FDA's final guidance on *Interpretation of the "Deemed to be a License" Provision of the Biologics Price Competition and Innovation Act of 2009,*[4] "an original 505(b)(2) application (including a resubmission) for a biological product that relies, at least in part, on FDA's finding of safety and/or effectiveness for a listed drug that is a biological product will receive a complete response if the application is pending at the end of the day (11:59 pm Eastern Daylight Time (EDT)) on Friday, March 20, 2020, because the NDA for the listed drug relied upon will no longer exist at midnight on Monday, March 23, 2020."

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

[4] Available at https://www.fda.gov/media/119590/download

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.[5]

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Michael G. White, Ph.D., Senior Regulatory Project Manager, at (240) 402-6149.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Deputy Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

[5] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
08/28/2019 02:50:21 PM