IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

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

AVADEL'S BRIEF IN OPPOSITION TO
PLAINTIFF'S MOTION FOR A STAY PENDING APPEAL

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STATUTES AND REGULATIONS

I. INTRODUCTION

With its latest motion, Jazz's strategy to delay at all costs reaches new heights. By refusing to delist the '963 patent even in the face of black-letter law, and by pursuing every conceivable source of delay in this litigation, Jazz has successfully—albeit illegally—excluded competition. No longer. In a thorough and well-reasoned opinion, this Court held that Jazz must request that the FDA delete the '963 patent from the Orange Book. That order is not only correct; it is important. Patients will no longer be deprived of Avadel's revolutionary, once-nightly sodium oxybate treatment, LUMRYZ.

Jazz's stay request seeks to render this Court's delisting order a dead letter. Given the timeline of Federal Circuit appeals, Jazz's proposal would effectively block delisting for the remaining lifetime of the '963 patent—*rewarding Jazz for its delay*. That result would undermine the very purpose of the delisting statute, penalize Avadel, and worse, harm the patients desperate for a once-nightly oxybate treatment for narcolepsy. Indeed, if Jazz wished to ensure sufficient time for an appeal of a delisting order before the '963 patent expired, why did Jazz insist that the delisting motion be delayed for over a year, oppose Avadel's motion to expedite consideration of it, D.I. 120; D.I. 165, and not seek to expedite even this motion to stay?[2] Jazz's motivation is, and has always been, to delay entry of LUMRYZ to protect Jazz's $5 million per day of oxybate products.

Jazz's machinations should not be rewarded, and Jazz's motion should be denied. The standard for such extraordinary relief is well established: Jazz must show a *strong likelihood* of success on appeal and that the equitable factors favor a stay. Jazz does not come close to meeting either of those requirements.

[2] All docket numbers refer to those in C.A. No. 21-691.

On the merits, the delisting statute could not be clearer that patents that do not claim either the drug or a method of using the drug qualify for delisting. Jazz persuaded the Court to delay resolution of Avadel's delisting motion until claim construction, and the intrinsic record revealed what is obvious on the face of the '963 patent—the claims are directed to systems. Following that ruling, the Court correctly found that the '963 patent should be delisted based on the plain language of the statute. Neither claim construction nor the application of the delisting statute to the properly construed claims was a close question, and Jazz has provided no basis for the Court to conclude that its rulings were in error.

Indeed, after months of asserting that the '963 patent claims are directed to "methods" despite their plain language to the contrary, including successfully postponing consideration of Avadel's motion for a year on the theory that it required claim construction, Jazz now has done an about-face. On appeal, Jazz contends claim construction is irrelevant and indicates that it does not seek review of the *Markman* Order. Ex. A. And after two full rounds of briefing before this Court on Avadel's delisting motion, Jazz now raises multiple new arguments in its motion for a stay. This has gone on for long enough. The Court rejected Jazz's efforts to delay as well as Jazz's efforts to argue that the '963 patent should not be delisted. The Court should not now hand Jazz a victory by allowing it to moot by delay the Court's order on Avadel's delisting motion.

The public interest also overwhelmingly militates against further delay. Much as Jazz may recoil from it, competition serves the public interest. The FTC's amicus brief on the delisting motion made clear that REMS patents like the '963 patent should never be used to keep competitive products off the market; that is even more true when the new product offers a significant therapeutic benefit for patients. Narcolepsy patients want and need a drug that will

allow them to sleep through the night, and Jazz's most recent effort to block their access to such a drug should be denied.

II. ARGUMENT

In assessing Jazz's stay requests, the Court considers four factors: "'(1) whether the stay applicant has made a strong showing that he is likely to succeed on the merits; (2) whether the applicant will be irreparably injured absent a stay; (3) whether issuance of the stay will substantially injure the other parties interested in the proceeding; and (4) where the public interest lies.'" *Standard Havens Prod., Inc. v. Gencor Indus., Inc.*, 897 F.2d 511, 512 (Fed. Cir. 1990) (quoting *Hilton v. Braunskill*, 481 U.S. 770, 776 (1987)). These factors effectively require the Court to consider "movant's chances for success on appeal and weigh[] the equities as they affect the parties and the public." *Id.* at 513. The "less likely [the applicant] is to win, the more need" for equitable factors to "weigh in [its] favor." *Id.* This test is similar to that used to evaluate a request for an injunction pending appeal, *see Duramed Pharms., Inc. v. Watson Lab'ys, Inc.*, 426 F. App'x 905, 906 (Fed. Cir. 2011), and, accordingly, Avadel relies in part on injunction case law.

A. Jazz's Strategic Machinations Warrant Denial of Its Motion

A party seeking the extraordinary equitable relief of a stay should come to the Court with clean hands. But Jazz has done the opposite by delaying resolution of this issue at every turn, and, with regard to this motion, manipulating proceedings to justify seeking an emergency stay from the Federal Circuit.

Jazz waited several days after entry of the Court's delisting order to even raise the prospect of a stay. *See* D.I. 230; Ex. B. When it finally did, Jazz made no mention of expedited briefing. *See* Ex. B. Nor did Jazz do so when the parties met and conferred, insisting it would follow the default local rules when counsel for Avadel expressly raised the issue. Ex. C. Jazz then filed its motion, which contains no request to expedite briefing. *See* D.I. 235, 236. The Court then *sua*

sponte expedited Avadel's Opposition, ordering it to be filed December 1. D.I. 237. The rationale for Jazz's inaction has now become clear – Jazz delayed and avoided seeking expedited briefing so it can purport to have a basis to "file an emergency motion for stay in the Federal Circuit early next week." D.I. 238 at 1.

On Sunday, November 27, 2022, Jazz wrote to Avadel's counsel indicating that it intends "to seek an emergency motion to stay the District Court's order at the Federal Circuit if the District Court does not act on Jazz's request for a stay by tomorrow afternoon." Ex. D. But Jazz never asked this Court to expedite briefing or consideration of its motion, let alone on a schedule that allowed it to be acted on by November 28th. Instead, Jazz waited until Tuesday, November 22nd at 6:23 p.m. to file its motion, Ex. E, knowing the Court was closed for Thanksgiving November 24th and 25th, and has told the Federal Circuit that it needs emergency relief if the Court does not rule on November 28th – before the date initially set by the Court for Avadel's Opposition, Ex. A. Jazz refrained from seeking expedited briefing and consideration from this Court so it could feign impracticability to the Federal Circuit and usurp this Court's original jurisdiction. Jazz's motion should be denied on that basis alone. *See Newimar, S.A. v. United States*, No. 21-cv-1897, 2022 WL 17072803, at *3 (Fed. Cl. Nov. 17, 2022).

B. Jazz Fails To Establish The Requisite "Strong Showing" That it is Likely to Prevail on Appeal

As noted, a stay pending appeal is an extraordinary remedy such that Jazz has to establish "a strong showing that [it] is likely to succeed on the merits." *Standard Havens*, 897 F.2d at 512. Jazz cannot possibly meet this burden.

1. The Court Correctly Decided That The '963 Patent Should Be Delisted Based On The Language Of 21 U.S.C. § 355(c)(3)(D)(ii)(I)

The Court correctly found that the '963 patent does not claim "an approved method of using the drug" for the simple reason that it is directed to a system, and accordingly required Jazz

to request that it be delisted from the Orange Book. *See* D.I. 231 at 6. Jazz's attempts to inject confusion and complexity into that straightforward determination are unlikely to be any more successful before the Federal Circuit than they were before this Court.

The delisting statute is clear. An NDA holder can be required to delete patent information from the Orange Book "on the ground that the patent does not claim either—(aa) the drug for which the application was approved; or (bb) an approved method of using the drug." 21 U.S.C. §355(c)(3)(D)(ii)(I). Jazz concedes that the '963 patent does not claim the drug. It also does not claim a method of using the drug – it claims no method of anything. As the Court correctly found, the "claims of the '963 patent are directed to systems." D.I. 231 at 6; D.I. 229 at 14-17.

Remarkably, after a year of delay allegedly due to the need for claim construction to resolve Avadel's delisting motion, Jazz *does not challenge the Court's claim construction* for the purposes of its stay motion (nor does Jazz challenge it in the Federal Circuit). D.I. 236 at 6; Ex. A. That concession ends the inquiry, as the '963 patent's *system* claims cannot be "an approved *method* of using the drug." The Court properly construed and applied the plain language of the statute, consistent with the First Circuit's ruling in *In re Lantus Direct Purchaser Antitrust Litig.*, 950 F.3d 1 (1st Cir. 2020), to find that the patent must be delisted. That analysis is hardly the type of clear error Jazz would have to establish to show a "strong likelihood" of success on appeal.

Jazz's argument that the de-listing statute exempts from its scope patents that were "permissively listed" contradicts the unambiguous language of the delisting statute, which plainly states that patents that do not fall into one of two specific categories should be delisted. *The statute does not require an inquiry into whether the NDA holder was authorized to list the patent in the first instance*. Rather, the '963 patent is subject to delisting because it "does not claim . . . *an approved method of using the drug*." 21 U.S.C. § 355(c)(3)(D)(ii)(I). Statutory construction begins

"with the language of the statute." *Kingdomware Techs., Inc. v. United States*, 579 U.S. 162, 171 (2016). And when the language of that statute is clear, the Court's inquiry "ends there as well." *Hughes Aircraft Co. v. Jacobson*, 525 U.S. 432, 438 (1999). Congress could have required a movant to make a showing that the '963 patent was not appropriately "included in the Orange Book under the law that applied at the time of their listing" but did not do so. The Court must enforce the statute according to its plain meaning. *See Rotkiske v. Klemm*, 140 S. Ct. 355, 360 (2019) ("If the words of a statute are unambiguous, this first step of the interpretive inquiry is our last.").

*N*o court has adopted Jazz's view that the delisting statute in any way depends on the propriety of listing. As the Supreme Court recognized in *Caraco*, an NDA applicant sued for patent infringement may "assert a counterclaim seeking an order requiring the [brand] to correct or delete the patent information submitted by the [brand] under subjection (b) or (c) of § 355 on the ground that the patent does not claim either" a "drug" or "an approved method of using the drug." *Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 408-409 (2012) (citing 21 U.S.C. § 355(j)(5)(C)(ii)(I)). That is what Avadel did and what this Court correctly found. No further analysis is warranted.

2. Jazz's Disputes With The Court's Ruling Do Not Establish A Strong Likelihood Of Success On Appeal

Jazz's motion includes nearly ten pages disputing the Court's decision. Those arguments were either already rejected or are entirely new and waived (both for purposes of this motion and for appeal), and thus cannot show a likelihood of success on appeal. Even if considered, Jazz's new arguments likewise fail to show that Jazz is likely to succeed on appeal.

a. The Court Correctly Rejected Jazz's Argument that the Delisting Statute Does Not Apply To So-Called "Permissively-Listed" Patents

As noted, the de-listing statute requires no inquiry into whether or not the '963 patent was appropriately listed by Jazz at the time of its listing. But Jazz's contention that the '963 patent was properly listed is erroneous in any event.

First, Jazz's argument is wholly inconsistent with the First Circuit's decision in *Lantus*. D.I. 154 at 6 (*citing* 950 F.3d 1). The patent at issue there was listed in the Orange Book in 2013, prior to the passage of the Orange Book Transparency Act ("OBTA"), just like the '963 patent. 950 F.3d at 5. The *Lantus* patent covered a drive mechanism for enabling administration of medicinal products from an injector pen, such as those used to administer insulin. *Id*. *Under Jazz's theory, such a patent would be permissibly listed* in the Orange Book because it does not fall into the categories prohibited from listing by 21 C.F.R. § 314.53(b)—patents on processes, packaging, metabolites, and intermediates. D.I. 236 at 7. However, the First Circuit found otherwise.

Second, Jazz's assertion that, before the passage of the OBTA, the listing statute allegedly permitted any patent to be listed in the Orange Book (other than a few narrow categories of patents that are explicitly prohibited) makes no sense in the context of the overall statutory scheme. The plain language of the pertinent statutes reveals that they are in perfect harmony. The listing statute provides that any patent that "claims the drug for which the applicant submitted the application" or "claims a method of using a drug for which approval is sought or has been granted in the application" shall be listed in the Orange Book. 21 U.S.C. § 355(b)(1)(A)(viii). The listing statute's requirement that NDA applicants "*shall*" list each patent claiming a drug or "a method of using [a] drug" is meant to be an exclusive list. *See, e.g.*, *Carcieri v. Salazar*, 555 U.S. 379, 391-92 (2009) (holding that where Congress directed that the definition of "Indian" for purposes of the Indian Reorganization Act "shall" include persons meeting three discrete qualifications, Congress

"explicitly and comprehensively defined the term" by reference to those qualifications). The delisting statute, in turn, states that patents that do not fall into either of those categories—*i.e.*, patents that do not claim either "the drug for which the application was approved" or "an approved method of using the drug"—are eligible for delisting. 21 U.S.C. §355I(3)(D)(ii)(I). Read together, Congress provides that patents that do not claim either a drug or method of using a drug can be delisted pursuant to 21 U.S.C. §355(c)(3)(D)(ii)(I) as they were not appropriately listed in the first place. *See, e.g., Lantus*, 950 F.3d at 7; *Caraco*, 566 U.S. at 408-09. The plain meaning of each statute shows that they are in harmony.

Third, Jazz's assertion that, before the passage of the OBTA, the listing statute allegedly permitted the '963 patent to be listed in the Orange Book and correspondingly exempted from delisting would flout this well-integrated statutory scheme. The delisting statute was enacted in 2003 and Jazz did not list the '963 patent until a decade later. Jazz's theory would render that 2003 enactment dead-letter as to the '963 patent (and other categories), an absurd result directly contrary to the Supreme Court's elucidation of the purpose of the delisting statute, which was to alleviate "abuses" from brand companies, where "a brand whose original patent on a drug was set to expire listed a new patent ostensibly extending its rights over the drug, but in fact covering neither the compound nor any method of using it." *Caraco*, 566 U.S. at 408. Given the backdrop, Jazz's theory cannot be correct. *See Nat'l Ass'n of Mfrs v. Dep't of Defense*, 138 S. Ct. 617, 632 (2018) (rejecting "an interpretation of the statute that would render an entire subparagraph [of the statute] meaningless").

Indeed, the OBTA's mandate that "[p]atent information that is not the type of patent information required by subsection (b)(1)(A)(viii) shall not be submitted" is merely a clarification. FDA and Congress have confirmed that the OBTA was amended to "clarify[] the types of patent

and exclusivity related information to be listed in" the Orange Book in a Report to Congress. Ex. F (FDA Report to Congress) at 1; *see also id*. ("These revisions were generally consistent with the existing regulations and practices of [FDA]."); Ex. G (H.R. 116-47) at 7 ("[T]he general performance goal or objective of this legislation is to amend the [FDCA] to clarify which patents should be submitted to FDA. . . ."). Accordingly, the Federal Circuit is unlikely to agree with Jazz that the OBTA was intended "to narrow," rather than clarify, "the universe of patents that are appropriately listed." D.I. 236 at 6. Jazz's suggestion that the Court strain to identify ambiguity where none exists stands statutory construction on its head. This Court's "task is to fit, if possible, all parts into a harmonious whole." *Roberts v. Sea-Land Servs., Inc*., 566 U.S. 93, 100 (2012).

Fourth, Jazz's reading is inconsistent with the First Circuit's *Lantus* decision. There, the First Circuit found that "[t]he statute and applicable regulations call for the listing of *only* patents that claim the pertinent drug or a method of using the drug." *Lantus*, 950 F.3d at 7; *see also id*. at 10. The Court determined that because the patent at issue did not claim a drug product or method of using a drug "it was improper for Sanofi to have submitted it for listing in the Orange Book." *Id*. at 8. Thus, *Lantus* is directly at odds with Jazz's theory that patents could be "permissibly" listed in the Orange Book before the OBTA even if they did not fall into one of the categories of patents recited in the listing statute. The Federal Circuit likely will agree.

Fifth, the basis for Jazz's theory that listing is proper (and thus that delisting is improper) is *a regulation*:

> Jazz was at least *permitted* to list the '963 patent in 2014 because the '963 patent does not fall into one of the categories that the FDA—in interpreting and implementing the Orange Book listing statute—prohibited from being listed in 21 C.F.R. § 314.53(b)(1).

D.I. 236 at 6-7. In short, Jazz alleges that the FDA's regulation effectively creates a conflict with the plain language of the listing and delisting statutes. But a regulation cannot upend the plain

language of a Congressional statute and were Jazz correct that the regulation was in any way inconsistent with the statutes, it would be void. *See GHS Health Maint. Org., Inc. v. United States*, 536 F.3d 1293, 1297 (Fed. Cir. 2008) ("When a regulation directly contradicts a statute, the regulation must yield.").

That precept likewise disposes of Jazz's contention that its listing was permissible because "[t]here is no question that FDA has primary jurisdiction to interpret and execute the FDCA, including the portions of section 505 that govern the Orange Book." D.I. 236 at 7. To be clear, whether listing was permissible is of no moment, because, as described above, delisting does not depend on permissible listing. Congress alone determines what a counterclaimant must prove to establish delisting and did so plainly and unambiguously. *See supra* at § II.B.1. Any purported FDA regulation or guidance to the contrary would be void on its face.

Worse, Jazz's argument contradicts the delisting statute in another fundamental sense – the salient inquiry is whether "the patent does not *claim*" an "approved method of using the drug." 21 U.S.C. § 355(c)(3)(D)(ii)(i). This Court alone determines what a patent "claims." *Caraco*, 566 U.S. at 406 ("[T]he courts are the appropriate mechanism for the resolution of disputes about the scope of validity of patents."). The FDA itself emphasizes it has no expertise whatsoever in construing patent claims, and as the Supreme Court noted in *Caraco*, FDA "does not independently assess the patent's scope," and makes no determinations regarding delisting, which is the exclusive province of the district court. *Id.* at 406. Hence, Jazz's suggestion that the Federal Circuit is "likely" to defer to "the current policy of the expert federal agency with primary jurisdiction," D.I. 236 at 9, makes no sense.

b. Jazz's New Argument that the '963 Patent's System Claims Nevertheless Cover Methods Does Not Present "Strong" Grounds for Success on Appeal

Jazz next relies on the entirely new argument that, even though the '963 patent claims are directed to "systems," they are nevertheless properly listed in the Orange Book because the patent term "method" allegedly means something different than the term "method" as used in the delisting statute. D.I. 236 at 8-15. This argument is both waived and plainly erroneous.

First, Jazz waived this argument. Jazz filed no fewer than four briefs in opposition to Avadel's motions, none of which assert that system claims can nevertheless constitute methods of using a drug within the meaning of the delisting statute. As this Court correctly pointed out, Jazz advanced "no theory that the '963 patent, construed as claiming systems, could constitute 'an approved method of using the drug.'" D.I. 231 at 6. Jazz has now waived any such argument, *see Align Tech., Inc. v. 3Shape A/S, No. CV 17-1648-LPS*, 2021 WL 1535530, at *6 (D. Del. Apr. 19, 2021), *report and recommendation adopted sub nom. Align Tech., Inc. v. 3Shape A/S & 3Shape Inc.*, No. CV 17-1648-LPS, 2021 WL 7412181 (D. Del. May 28, 2021) (finding defendant's failure to present an argument in its briefing constitutes waiver), and is unlikely to succeed on its argument for that reason alone. *ViaTech Technologies Inc. v. Microsoft Corporation*, 733 Fed. App'x. 542, 552 (Fed. Cir. 2018).[3]

Jazz's argument is also meritless, as it turns on the allegation that there is "no evidence that Congress meant the word 'method' to import patent-law concepts into the FDCA." D.I. 236 at 10. That is baseless. On its face, the delisting statute requires an inquiry into what an Orange Book-listed patent "*claims*." 21 U.S.C. § 355(c)(3)(D)(ii)(I). As the Supreme Court emphasized, "construing the patent" is "a question of law, to be determined by the Court." *Markman v.*

[3] If Jazz's belated argument is truly strong enough to establish a likelihood of success, one wonders why Jazz failed to raise it sooner. And if as Jazz now contends, a "system" claim is nevertheless a "method" within the meaning of the delisting statute, one wonders why Jazz fought to construe the '963 patent claims as methods (in the patent context). Both questions answer themselves.

Westview Instruments, 517 U.S. 370, 384 (1996). The inquiry as to whether the '963 patent "does not *claim* . . . an approved method of using the drug" is thus one for the Court utilizing claim construction principles. 21 U.S.C. § 355(c)(3)(D)(ii)(I)(bb). Because "[w]e generally presume that Congress is knowledgeable about existing law pertinent to the legislation it enacts," *Goodyear Atomic Corp. v. Miller*, 486 U.S. 174, 184-85 (1988), the delisting statute plainly contemplates and applies patent terminology as understood in the context of patent law. The natural reading of the statute is therefore that Congress intended for the phrase "claim . . . an approved method" to be interpreted according to patent law principles.

Further, Jazz's assertion that "the controlling FDA regulation *proves* that patent law definitions *cannot* apply" by forbidding the submission of process patents is incorrect. D.I. 236 at 10 (emphasis in original). First, this argument fails because, at best, it would have an FDA regulation trump a congressional statute. *GHS Health*, 536 F.3d at 1297 ("When a regulation directly contradicts a statute, the regulation must yield."). Second, the term "process" as used in 21 C.F.R. § 314.53(b)(1) does not refer to methods generally, as Jazz contends—it refers to patents for manufacturing processes. *See* Ex. F (FDA Report to Congress) at 6 ("In response to a comment suggesting that clarification was needed on whether patent information on *manufacturing processes* is appropriate for submission to FDA, the preamble to the final rule reiterated that the regulation at 21 CFR 314.53(b) clearly states that information on *process patents* should not be submitted to FDA").

Jazz's suggestion that "approved methods of using [a] drug" are allegedly synonymous with the "indications or other conditions of use for which approval is sought or has been granted" is also incorrect. D.I. 236 at 11. Jazz quotes from an FDA regulation that limits what information must be listed in the Orange Book, leaving out the beginning of the sentence which states that it

applies to "*patents that claim a method of use*." 21 C.F.R. § 314.53(b)(1) ("For patents that claim a method of use, the applicant must submit information only on those patents that claim indications or other conditions of use for which approval is sought or has been granted.") Because the '963 patent does not claim a method of use, it does not claim any subset like a condition of use.

In any event, the FDA has not interpreted the term "approved methods of using [a] drug" in the listing and delisting statutes to mean "conditions of use." D.I. 236 at 11. Rather, FDA has previously explained in federal court its "longstanding" and "consistent view" is that a "condition of use" is strictly limited to "how, to whom, and for which purposes the drug is *administered*." *ViroPharma, Inc. v. Hamburg*, No. 1:12-cv-00584-ESH (D.D.C. Sept. 4, 2012), ECF No. 53. As FDA told the court, "'[c]onditions of use' thus include a drug product's indications and dosing regimen," but do not include all contents of a drug product's labeling." *Id.* at 19-20. The '963 patent is not a condition of use pursuant to FDA's explicitly stated definition.

Jazz's reliance on so-called "ordinary speech" to try and establish that a "system" includes a "method" utterly fails. D.I. 236 at 10. Rather than look to patent law concepts for the meaning of "method of use," Jazz points the Court to a 1999 district court case from West Virginia, Black's Law Dictionary, and an International Dictionary. *Id*. How or why Jazz chose these disparate and haphazard references remains unstated. Were the Court to go down this road (and it should not), other dictionary definitions contradict Jazz's interpretation of the terms "system" and "method." Merriam-Webster's dictionary defines "method" as "a procedure or process for attaining an object," Ex. H, and "system" as "a regularly interacting or independent group of items forming a unified whole," Ex. I. This is consistent with how the terms "method" and "system" are used in patent law and does not indicate that these two terms are used "interchangeably" as Jazz argues. D.I. 236 at 10. While the Federal Circuit is exceedingly unlikely to determine that the term

"method" in the delisting statute means something different than what it means in the patent law context, it is equally unlikely to rely on Jazz's cherry-picked definitions. *Id.*

Finally, Jazz's attempt to heighten the importance of the questions allegedly raised by its appeal falls flat. Lantus already decided that a patent should not have been listed in the Orange Book prior to the OBTA if it neither claims the drug nor an approved method of using the drug. The Federal Circuit is most unlikely to view the additional questions raised by Jazz's appeal as new, important questions given that the crux of Jazz's argument is that a patent construed to cover "systems" is a "method of using [a] drug" pursuant to 21 U.S.C. § 355(c).

C. The Equities Resoundingly Disfavor A Stay

1. Jazz Has Not Shown That It Will Be Irreparably Harmed

Because Jazz fails at the likelihood of success prong, it "would need to make a stronger showing of irreparable harm to succeed on this motion." *Sciele Pharma Inc. v. Lupin Ltd.*, No. CIV. 09-0037 RBK/JS, 2012 WL 113004, at *3 (D. Del. Jan. 12, 2012). Jazz argues it will be irreparably harmed because it will not be able to re-list its patent in the Orange Book if it prevails on appeal, because the patent will have expired. But "the possibility that an appeal may become moot does not alone constitute irreparable harm for purposes of obtaining a stay." *In re THG Holdings LLC*, Nos. 19-11689 (JTD), 19-2215 (RGA), 2019 WL 6615341, at *6 (D. Del. Dec. 5, 2019).

Further, while Jazz claims irreparable harm due to the "expir[ation]" of the '963 patent "while the appeal is pending" D.I. 236 at 3), Jazz has only itself to blame for the timing of this Court's decision, having persuaded the Court to defer ruling on delisting for a year. Jazz can hardly base its claim of irreparable harm on circumstances of its own creation. *See Otsuka Pharm. Co. v. Torrent Pharms. Ltd., Inc.*, 99 F. Supp. 3d 461, 505 (D.N.J. 2015).

In the end, Jazz's arguments on harm to Jazz and to Avadel are in irreconcilable conflict. Jazz's claim of irreparable harm is predicated on a potential "loss of pediatric exclusivity." D.I. 236 at 15. But that presumes LUMRYZ is fully approved and marketed – otherwise Jazz will not suffer any harm as a result of any purported loss of exclusivity. Indeed, in its next breath, Jazz maintains that no harm will befall Avadel because LUMRYZ "cannot be lawfully marketed even if Jazz delists the '963 patent" because of the ostensible "protections of Orphan Drug Exclusivity." D.I. 236 at 16. If LUMRYZ truly cannot be lawfully marketed even if Jazz delists the 963 patent, then Jazz will suffer no harm even in the absence of a stay.

2. Avadel Will Be Irreparably Harmed by a Stay

The real reasons Jazz wants a stay is to keep LUMRYZ from getting final FDA approval and keep Avadel from selling LUMRYZ. *See* D.I. 236 at 3 (arguing lack of a stay will make it hard for Jazz "to recover the stay of approval that is currently in force"). Being prevented from getting final approval and being prevented from selling LUMRYZ are, unquestionably, harms to Avadel, and on that basis alone, the Court can find the equities favor Avadel and not Jazz. Should the Court have any question on that issue, Avadel's CEO, Greg Divis, explains some of the ways the delay in FDA approval has caused harm to Avadel, including that Avadel cannot fund R&D projects it would fund if it had revenue from LUMRYZ sales. These types of harms are irreparable. *See, e.g.*, *Vanda Pharms. Inc. v. Roxane Lab'ys, Inc.*, 203 F. Supp. 3d 412, 436 (D. Del. 2016), *aff'd*, 887 F.3d 1117 (Fed. Cir. 2018) (being unable to use lost revenue to invest in R&D irreparable).

Jazz's attempts to get this Court to ignore the harm to Avadel do not survive scrutiny.

First, Jazz observes that the final orphan drug exclusivity ("ODE") determination has not yet been made and suggests Avadel might not be able to launch as a result. Jazz's delay in removing the '963 patent from the Orange Book is the reason why Avadel has not yet been able

to get a final ODE ruling. As Avadel's regulatory expert explains, it is FDA policy not to communicate a final decision on ODE until final approval, and thus "FDA's silence to date is to be expected" and is not evidence that LUMRYZ's approval will be delayed. Cook Decl. ¶ 7. Jazz cannot rely on the lack of that ODE determination as a reason for granting the equitable relief of a stay—Jazz is the reason that decision is delayed, and its hands are not clean.

Second, in a single sentence, Jazz asserts that the other patents in suit must be adjudicated before LUMRYZ can be marketed. Not so. Products are routinely sold during the pendency of patent lawsuits. Jazz does not practice the other six patents in this suit (because Jazz does not have a once-nightly narcolepsy product), they are not listed in the Orange Book, and thus did not trigger any automatic stay of approval of Avadel's NDA. If Jazz wanted this Court to enjoin the sale of LUMRYZ, it needed to move for a preliminary injunction and meet the high bar for such extraordinary relief. Jazz has not done so (even though Avadel repeatedly offered to negotiate a schedule so any such motion could be resolved in an orderly fashion). D.I. 71. Jazz's apparent reluctance to file for an injunction[4] presumably reflects its recognition that it would be exceedingly unusual to enjoin the sale of a highly differentiated medicine that could be transformational for patients. *See infra*, Section II.C.3. Accordingly, the fact that there are other patents in this suit has no bearing on the harm to Avadel that would be imposed by a stay.

Finally, Jazz's arguments about when Avadel filed a patent certification for the '963 patent are just another distraction. Avadel followed the statutory framework by filing a counterclaim promptly to have the offending patent removed from the Orange Book. For Jazz to suggest Avadel's *successful* litigation strategy was so wrong as to warrant ignoring the harm to Avadel that would result from a stay of that order is nonsensical.

[4] When asked directly by Avadel's counsel, Jazz did not confirm it intended to move for a P.I.

3. The Public Interest Will Be Harmed by a Stay

It is not equitable to grant relief that will harm patients. *See Baxalta Inc. v. Genentech, Inc.*, No. 17-509-TBD, 2018 WL 3742610, at *12-13 (D. Del. Aug. 7, 2018); *Abbott Cardiovascular Sys., Inc.*, No. 19-149 (MN), 2019 WL 2521305, at *25 (D. Del. June 6, 2010); *Bianco v. Globus Med., Inc.*, No. 12-CV-00147, 2014 WL 1049067, at *11 (E.D. Tex. Mar. 17, 2014) (collecting cases). Dr. Bruce Corser, a doctor focusing on sleep medicine, explains that narcolepsy is a serious and chronic disorder. Corser Decl. ¶ 4. Oxybate is useful in treating narcolepsy, but for the last twenty years has only been available as a twice-nightly product. *Id.* at ¶¶ 6-8. As a result, patients suffering from a chronic sleep disorder will never get a full night's sleep, because each and every night, the patient must wake up to take a second dose. Corser Decl. ¶ 8. Patients can and do sleep through their middle-of-the-night alarm. Corser Decl. ¶¶ 12-14. And patients who wake up late for their second dose are faced with a "terrible dilemma": skip the second dose and experience uncontrolled and potentially dangerous narcolepsy and cataplexy, or take the dose and be late to school or work. Ex. K (Gudeman Dep.) at 33:3-35:21;[5] *see also* Corser Decl. ¶¶ 9, 12; Gudeman Decl. ¶¶ 6, 8, 11. Narcolepsy patients can experience such difficulty in consistently waking up at the right time that loved ones sometimes take on the role of waking up every night to wake up the patient, such that they, too, can never get a full night's rest. Gudeman Decl. ¶ 11; Ex. K at 35:10-12. Narcolepsy patients and their caregivers deserve a once-nightly treatment.

Drug safety is also an issue with Jazz's products, as the second dose of oxybate—a controlled substance with abuse potential—is left out on the nightstand to be taken by the patient

[5] Dr. Jennifer Gudeman is the Vice President, Medical and Clinical Affairs at Avadel Pharmaceuticals.

during the night while still in bed. Corser Decl. ¶ 17. Access by children or roommates can pose a significant danger. *Id.* at ¶¶ 16-17.

These challenges have caused some patients to stop taking Xyrem or Xywav, or to never start at all. *See* Corser Decl. ¶¶ 18-20; Gudeman Decl. ¶ 7; Ex. K at 46:20-47:16, 71:13-22. Research has concluded there is an "urgent need for a once-at-bedtime sodium oxybate therapy." Gudeman Decl. ¶¶ 9-11; Gudeman Decl., Ex. A ("TREND Ltr.") at 1. High numbers of patients reported issues with the timing of the middle-of-the-night dose, leading to injuries, mental health issues, and termination of employment. Gudeman Decl., Ex. A at 1-2. Patients urge that FDA approve a once-nightly option without further delay, *see id.* at 2-7. Every additional day of delay in getting LUMRYZ approved and on its way to patients is a harm to the public interest.

Jazz's brief says not one word about the harm to these narcolepsy patients whose lives stand to be greatly improved by LUMRYZ. Instead, Jazz hides behind its argument that approval might not actually be imminent. But if Jazz is correct that LUMRYZ will not be approved for other reasons, then there is no need to grant a stay. The only effect of a stay is to prevent Avadel from launching LUMRYZ, thus preventing patients to benefit from it.

The public interest in protecting IP rights does not outweigh the public interest in protecting patients. In the *Baxalta* case, after recognizing the importance of patent rights, Judge Dyk found a preliminary injunction was against the public interest "given the ample evidence of medical need" and "unique medical benefits not available from [the plaintiff's] competing products." 2018 WL 3742610, at *12. So too here. *See Apple Inc. v. Samsung Elecs. Co.*, 735 F.3d 1352, 1372–73 (Fed. Cir. 2013) (holding district court properly considered, in public interest fact, the scope of the requested injunction "relative to the scope of the patented features and the prospect that an injunction would have the effect of depriving the public of access to a large number of non-

infringing features."). Indeed, Congress could have, but did not, provide for expedited appeals and/or a stay in the case of an order de-listing a patent. And the public has an interest in stopping anticompetitive misuses of the Orange Book. *See* D.I. 227 at 14-15 (FTC amicus brief discussing harm to the public from an improper Orange-Book listing and the abuse of REMS patents).

There is a clear and urgent need for LUMRYZ. On the strength of this factor alone, Jazz's motion should be denied.

D. Jazz's Alternative Request for a 30-Day Stay Should Be Denied

Jazz's alternative request for a 30-day stay fares no better. The same factors all apply to warrant denial of that alternative request. Jazz's cases are not to the contrary. In *DePuy*, for example, the stay pending appeal related to whether a document should be made public and did not cause the kind of grave harm that will result from a stay here. *DePuy Synthes Prod., Inc. v. Veterinary Orthopedic Implants, Inc.*, 990 F.3d 1364, 1367 (Fed. Cir. 2021). Indeed, the stay granted in *Galderma* shows why Jazz should lose its motion. Defendant Teva won below and thereafter launched its generic product. Plaintiff Galderma—the party in Jazz's shoes—convinced the court to prevent Teva from acting on its victory and obtained an injunction pending Galderma's appeal. The Federal Circuit then stayed *that* injunction, permitting Teva to sell its product during the appeal. *Galderma Lab'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 842 (Fed. Cir. 2020).

Finally, Jazz could have sought expedited consideration in this Court and then filed an emergency motion for a stay in the Federal Circuit that could have been resolved without the need for this extraordinary relief. *See supra* Section II.A. Jazz wants a thirty-day stay because that is thirty more days Jazz can avoid competition from LUMRYZ—compare the thirty days sought by Jazz to get that motion on file to the *four days* granted in one of Jazz's primary authorities. *See*

Takeda Pharms. U.S.A., Inc. v. Mylan Pharms., Inc., No. CV 19-2216-RGA, 2020 WL 419488, at *3 (D. Del. Jan. 27, 2020).

E. Jazz Has Not Met the Requirement for a Bond

Jazz's request for a stay pending appeal is governed by Fed. R. Civ. P. 62(d), which permits a court to suspend or modify an injunction pending appeal "on terms for bond or other terms that secure the opposing party's rights." Jazz fails even to mention this requirement or explain how it proposes to satisfy it. That failure itself warrants rejecting Jazz's motion. But even were it otherwise, Jazz would have no basis for objecting to Avadel setting the amount. Based on Jazz's $5 million in revenue per day on oxybate sales, *see* Divis Decl. ¶ 21, a bond in the amount of approximately $1 million per day for the duration of the stay[6] would provide an appropriate level of security for Avadel pending the outcome of the appellate process.

III. CONCLUSION

Jazz's motion for a stay—of either the length of an appeal or 30 days—should be denied.

[6] The bond amount for a 30-day stay would be $30 million.

Dated: November 29, 2022

MCCARTER &ENGLISH, LLP

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EXHIBIT A

No. 23-1186

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

JAZZ PHARMACEUTICALS, INC.,
Plaintiff-Appellant,

v.

AVADEL CNS PHARMACEUTICALS LLC,
Defendant-Appellee.

Appeal from the United States District Court for the District of Delaware in No. 21-691, Honorable Gregory B. Williams

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PLAINTIFF-APPELLANT'S MOTION TO EXPEDITE PROCEEDINGS

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November 28, 2022

Counsel for Plaintiff-Appellant Jazz Pharmaceuticals, Inc.

CERTIFICATE OF INTEREST

Counsel for Jazz Pharmaceuticals, Inc., F. Dominic Cerrito, certifies the following:

1. **Represented Entities.** Provide the full names of all entities represented by undersigned counsel in this case. Fed. Cir. R. 47.4(a)(1).

   Jazz Pharmaceuticals, Inc.

2. **Real Party in Interest.** Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. Fed. Cir. R. 47.4(a)(2).

   None

3. **Parent Corporations and Stockholders.** Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. Fed. Cir. R. 47.4(a)(3).

   Jazz Pharmaceuticals plc.

4. **Legal Representatives.** List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

   Quinn Emanuel Urquhart & Sullivan, LLP: Andrew S. Chalson, Quentin Jorgensen, Nicholas LoCastro, Krista M. Rycroft, Evangeline Shih, Eric C. Stops

   Morris, Nichols, Arsht & Tunnell LLP: Jack B. Blumenfeld, Jeremy A. Tigan

5. **Related Cases.** Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5).

Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC, No. 1:22-cv-00941-GBW (D. Del.) (filed July 15, 2022).

6. **Organizational Victims and Bankruptcy Cases.** Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

Not applicable

November 28, 2022

/s/ F. Dominic Cerrito

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Counsel for Plaintiff-Appellant Jazz Pharmaceuticals, Inc.

INTRODUCTION

Plaintiff-Appellant Jazz Pharmaceuticals, Inc. hereby moves to expedite briefing and consideration of Jazz's emergency motion for a stay pending appeal, filed concurrently with this motion, and for expedited briefing and consideration of the merits of the appeal.[1] Jazz appeals from an interlocutory order imposing a mandatory injunction. That injunction requires Jazz to request, on or before December 2, 2022, that the Food and Drug Administration de-list Jazz's '963 patent from FDA's Orange Book. Expedition is necessary to preserve the ability of this Court to provide meaningful relief given that Jazz's six-month pediatric exclusivity period—which the appealed-from order implicates—will evaporate and could not be revived in time before the appeal could be

[1] Pursuant to Federal Circuit Rule 27(a)(2), counsel for Jazz informed counsel for Defendant-Appellee Avadel CNS Pharmaceuticals LLP of Jazz's intent to file this motion. Counsel for Avadel informed counsel for Jazz that it does not oppose Jazz's request for an expedited briefing schedule on the merits of the appeal (or the specific schedule proposed), but it opposes the request for expedited briefing of the motion to stay, and it intends to file a response. Counsel for Avadel also asked that Jazz attach to this motion a copy of an email between counsel. That email is attached as Exhibit 1. Jazz disagrees with the characterizations made by counsel for Avadel in that email. In particular, there is no merit to Avadel's suggestion that Jazz somehow delayed seeking relief from the district court's 14-day deadline.

briefed and decided under the typical appeal schedule. Expediting the appeal will provide certainty to both parties regarding the listing of Jazz's '963 patent in the Orange Book.

BACKGROUND

This case arises out of Avadel's filing of an application for FDA approval of its proposed sodium oxybate drug product ("FT218"[2]) before the expiration of a number of Jazz-owned patents. Avadel's New Drug Application for its FT218 product was filed under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(b)(2), relying in part on FDA's prior approval of Jazz's Xyrem® product, which has the same active ingredient—sodium oxybate—as FT218.

Oxybate is a controlled substance (also known as gamma hydroxybutyrate or "GHB") and a strong central nervous system depressant. Today, to obtain FDA approval of a drug containing oxybate, the agency requires new drug applications to include a Risk Evaluation and Mitigation Strategy ("REMS"). Years ago, when Jazz first sought

[2] "LUMRYZ" is the proposed brand name for FT218. Because an unapproved new drug product like FT218 cannot be marketed in the United States, *see* 21 U.S.C. §§ 331(a), 355(d), it is more appropriate to refer to the drug by its investigational moniker.

FDA approval for Xyrem®, it developed a risk management program that was approved by FDA as a condition of use to ensure that Xyrem® could be safely brought to market. In 2007, Congress deemed that risk management program to be a REMS when it enacted the REMS statute, 21 U.S.C. § 355-1.

Jazz obtained a patent (U.S. Patent No. 8,731,963, or the "'963 patent") covering various elements of the risk management program (now REMS) for Xyrem®. The '963 patent has been included in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" publication (the "Orange Book") since 2014. The '963 patent is listed in the Orange Book under use code 1110 ("U-1110"), thereby protecting a "method of treating a patient with a prescription drug using a computer database in a computer system for distribution." *Avadel CNS Pharms., LLC v. Becerra*, No. 22-cv-02159 (APM), 2022 WL 16650467, at *3 (D.D.C. Nov. 3, 2023). Pursuant to a six-month extension as a result of the exclusivity Jazz received as a reward for establishing that sodium oxybate is safe and effective for use in pediatric patients, *see* 21 U.S.C. § 355a(b)(1)(B), the exclusivity associated with the '963 patent will last into June 2023, six months after the '963 patent itself expires.

In December 2020, Avadel applied for FT218's approval under FDCA section 505(b)(2) and relied on Xyrem® as the "listed drug" for that application. Avadel's strategy allowed it to rely on FDA's prior finding that Jazz's product is safe and effective, but it also required Avadel to provide a patent certification regarding each patent listed in the Orange Book for Xyrem®, including the '963 patent. *See* 21 U.S.C. § 355(b)(2)(A); 21 C.F.R. § 314.54(a)(1)(vi). Rather than submit such a patent *certification*, however, Avadel submitted a patent *statement*, declaring to FDA that its application did not seek approval for any protected use. *See* 21 U.S.C. § 355(b)(2)(B).

FDA rejected Avadel's filing strategy, concluding that Avadel's patent statement was not accurate. On May 24, 2022 the agency issued a decision explaining that Avadel sought "approval of a condition of use that is claimed by the '963 patent, as described by the U-1110 use code." *Avadel*, 2022 WL 16650467, at *3. Further, FDA explained that it would not approve Avadel's application unless Avadel replaced its inappropriate statement with a patent certification. *Id.* at *1, *3; *see* 21 U.S.C. § 355(d)(6); 21 C.F.R. § 314.125(b)(7). Avadel submitted the missing patent certification—and, as the statute requires, notified the

listed drug's patentholder, Jazz—and FDA provided a "tentative approval" on July 18, 2022. Complaint For Declaratory And Injunctive Relief at 5, *Avadel*, 2022 WL 16650467, ECF No. 1.

Jazz's receipt of Avadel's patent certification notice opened a 45-day window within which Jazz could allow the application's approval to be "made effective immediately," or else sue Avadel for patent infringement. 21 U.S.C. § 355(c)(3)(C). Jazz sued within the window, *see Jazz Pharms., Inc. v. Avadel CNS Pharms., LLC*, No. 1:22-cv-00941-GBW (D. Del.) (filed July 15, 2022), triggering a statutory thirty-month stay of approval. 21 U.S.C. § 355(c)(3)(C). The stay precludes approval of FT218 until expiration of the '963 patent's term and the related pediatric exclusivity in June 2023. *Id.* Jazz had previously sued Avadel on the '963 patent in the matter *Jazz Pharmaceuticals, Inc. v. Avadel CNS Pharmaceuticals, LLC*, No. 1:21-cv-00691-GBW (D. Del.) (filed May 12, 2021), and Avadel responded by (among other things) asserting a counterclaim seeking de-listing of the '963 patent. This appeal arises out of that Delaware case.

After Avadel's back-and-forth with (and patent certification to) FDA, Avadel filed claims in the U.S. District Court for the District of Columbia against multiple federal agencies and agency heads, including

FDA, seeking equitable relief. *See* Complaint For Declaratory And Injunctive Relief, *Avadel*, 2022 WL 16650467, ECF No. 1. Avadel claimed that FDA violated the Administrative Procedure Act by (1) "second-guess[ing] Avadel's decision to file a patent statement" and "compelling Avadel to submit a patent certification instead," *id.* at 24, and (2) unreasonably delaying approval of FT218, *see id.* at 25–26. Jazz intervened. Ultimately, the D.C. district court entered judgment against Avadel on its claims because of the "availability of adequate alternative relief" in the ongoing patent suit in the District of Delaware, *i.e.*, the proceedings below here. *See Avadel*, 2022 WL 16650467, at *2. Specifically, the D.C. district court observed that Avadel had available to it, and was already pursuing in the patent litigation, a statutory counterclaim seeking the delisting of the '963 patent.

About two weeks later, following Avadel's earlier request for expedited consideration of its delisting counterclaim, the Delaware district court in this case entered a mandatory injunction directing Jazz to submit to the FDA a request to delete the '963 patent from the Orange Book, on the ground that, in the district court's view, the '963 patent "does not claim … an approved method of using the drug" under 21 U.S.C.

§ 355(c)(3)(D)(ii)(I). As explained more fully in Jazz's concurrently filed motion to stay, the district court's decision was based on an erroneous interpretation of the relevant statutes, and its injunction—if not stayed—will cause Jazz irreparable harm.

Moreover, time is of the essence: The resolution of this dispute will determine whether Jazz will retain its statutory entitlement to a six-month period of pediatric exclusivity, running through June 17, 2023, based on expensive and valuable pediatric studies that Jazz conducted. As a practical matter, the appeal concerning Jazz's remaining six-and-a-half-months of exclusivity must be resolved expeditiously. That exclusivity period would be mostly or entirely consumed by the typical schedule for an appeal in this Court. Even more pressing is the deadline for Jazz to comply with the district court's injunction: absent further action by the district court or this Court, Jazz will need to send the request to "de-list" the '963 patent to the FDA by this Friday, December 2, 2022.[3] And if FDA were to act on that compelled de-listing request, Jazz's pediatric exclusivity would dissolve and likely could not be revived

[3] Jazz has moved the District Court for a stay but that court has not yet ruled.

even if this Court were to conclude on appeal that the injunction never should have been ordered.

ARGUMENT

Jazz respectfully requests expedited briefing and consideration of both its emergency motion for a stay and the merits of the appeal. Expedition is warranted because the standard timelines for briefing and consideration are impracticable in this case.

With respect to the emergency motion to stay, the standard briefing timeline would render the motion moot before it could be considered. Under Federal Rule of Appellate Procedure 27(a)(3)(A), Avadel's response would be due 10 days after service of the motion, *i.e.*, by December 8, 2022. But the injunction that Jazz seeks to stay requires Jazz to act by December 2, 2022.

Further, as explained more fully in Jazz's motion to stay the district court's mandatory injunction, if FDA *does* de-list the '963 patent in response to the action directed by district court, then Jazz's pediatric exclusivity will evaporate, and the patent and any associated exclusivity will expire on December 17, 2022 (before an appeal could plausibly be resolved). *See* Fed. R. App. P. 2 ("On its own or a party's motion, a court

of appeals may—to expedite its decision or for other good cause—suspend any provision of these rules in a particular case and order proceedings as it directs . . . .").

Accordingly, Jazz respectfully requests entry of the following briefing schedule for the motion to stay, or any other expedited schedule that the Court may order:

- Avadel's response: November 30, 2022
- Any reply by Jazz: December 1, 2022.

With respect to the merits of the appeal, expedition is warranted because the dispute concerns a six-month period of exclusivity—and thus a period that would likely begin and end during the course of an appeal briefed and argued on a typical schedule. As this Court recognizes, a motion to expedite "is appropriate where the normal briefing and disposition schedule may adversely affect one of the parties, as in appeals involving preliminary or permanent injunctions . . . ." Practice Notes to Fed. Cir. R. 27. Jazz already has taken steps to expedite by filing a notice of appeal within days of the entry of the injunction below, and Jazz is prepared to submit its briefs on an accelerated schedule to allow the appeal to be set for argument promptly (during the Court's February

2023 session, for example). To that end, Jazz respectfully requests entry of the following expedited schedule for briefing and consideration of the merits of this appeal or any other expedited schedule that the Court may order:

- Jazz's opening brief: December 16, 2022
- Avadel's response brief: January 13, 2023
- Jazz's reply brief: January 20, 2023
- Oral argument: during the Court's February session.

CONCLUSION

Jazz respectfully requests that its motion to expedite the proceedings on appeal be granted.

November 28, 2022

/s/ F. Dominic Cerrito

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATIONS

This motion complies with the word limit set forth in Fed. R. App. Pr. 27(d) because this motion contains 1,927 words.

This motion complies with the typeface requirements of Fed. R. App. Pr. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Word 365 in 14-point Century Schoolbook font.

November 28, 2022

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CERTIFICATE OF SERVICE

I hereby certify that on November 28, 2022, I electronically filed the foregoing using the Court's CM/ECF system, which will send notifications to all counsel registered to receive electronic notices, and served the foregoing by electronic mail to all counsel of record, at the addresses below.

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November 28, 2022

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Counsel for Plaintiff-Appellant Jazz Pharmaceuticals, Inc.

Exhibit

Exhibit

Document	Description
Exhibit 1	E-mail from Audra Sawyer, Latham & Watkins, to Gabriel P. Brier, Quinn Emanuel Urquhart & Sullivan (Nov. 28, 2022, 2:55 p.m. EST)

Exhibit 1

Gabriel Brier

From: Audra.Sawyer@lw.com
Sent: Monday, November 28, 2022 2:55 PM
To: Gabriel Brier; Herman.Yue@lw.com
Cc: KENNETH.SCHULER@lw.com; Marc.Zubick@lw.com; Sarah.Wang@lw.com; Sunnie.Ning@lw.com; Sarah.Propst@lw.com; DDurie@durietangri.com; KDavis@durietangri.com; ajoyce@mccarter.com; Nick Cerrito; Eric Stops; Evangeline Shih; Andrew Chalson; AJones@durietangri.com; Frank Calvosa; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel; DSilver@McCarter.com; Alex.Grabowski@lw.com; jazzpatentlitigation.lwteam@lw.com
Subject: RE: Jazz v. Avadel, No. 21-691

[EXTERNAL EMAIL from audra.sawyer@lw.com]

Gabe,

We are fine with the expedited schedule for briefing and consideration of the merits of Jazz's appeal that you set forth below—subject to the preferences of the Federal Circuit.

We otherwise object to your proposals for an emergency stay or an expedited briefing schedule thereon—especially given the very low likelihood of success on the merits of the appeal and Jazz's failure to exhaust its remedies in district court—and will respond in due course. We also reiterate our position that if Jazz truly wanted to seek all avenues of relief before the district court, it should have asked that court for expedited briefing and/or expedited relief. Jazz didn't do that. Instead, Jazz waited for the district court itself to propose an expedited schedule and only then decided that was not good enough. That does not justify emergency/expedited intervention by the Federal Circuit.

We ask that you attach this email to your Federal Circuit motion papers to accurately represent our position.

Thanks,

Audra

From: Gabriel Brier <gabrielbrier@quinnemanuel.com>
Sent: Monday, November 28, 2022 10:03 AM
To: Sawyer, Audra (DC) <Audra.Sawyer@lw.com>; Yue, Herman (NY) <Herman.Yue@lw.com>
Cc: Schuler, Kenneth (CH) <KENNETH.SCHULER@lw.com>; Zubick, Marc (CH/NY) <Marc.Zubick@lw.com>; Wang, Sarah (CH) <Sarah.Wang@lw.com>; Ning, Sunnie (BN) <Sunnie.Ning@lw.com>; Propst, Sarah (DC) <Sarah.Propst@lw.com>; DDurie@durietangri.com; KDavis@durietangri.com; ajoyce@mccarter.com; Nick Cerrito <nickcerrito@quinnemanuel.com>; Eric Stops <ericstops@quinnemanuel.com>; Evangeline Shih <evangelineshih@quinnemanuel.com>; Andrew Chalson <andrewchalson@quinnemanuel.com>; AJones@durietangri.com; Frank Calvosa <frankcalvosa@quinnemanuel.com>; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel <jazzavadel@quinnemanuel.com>; DSilver@McCarter.com; Grabowski, Alex (CH) <Alex.Grabowski@lw.com>; #C-M JAZZ PATENT LITIGATION - LW TEAM <jazzpatentlitigation.lwteam@lw.com>
Subject: RE: Jazz v. Avadel, No. 21-691

Audra,

We are available to meet and confer at 12:00 pm EST today. Please use the conference call information below:

Dial-in: (646) 518-9805
Meeting ID: 832 7728 4310
+16465189805,,83277284310#

Regards,

Gabe

From: Audra.Sawyer@lw.com <Audra.Sawyer@lw.com>
Sent: Monday, November 28, 2022 9:20 AM
To: Gabriel Brier <gabrielbrier@quinnemanuel.com>; Herman.Yue@lw.com
Cc: KENNETH.SCHULER@lw.com; Marc.Zubick@lw.com; Sarah.Wang@lw.com; Sunnie.Ning@lw.com; Sarah.Propst@lw.com; DDurie@durietangri.com; KDavis@durietangri.com; ajoyce@mccarter.com; Nick Cerrito <nickcerrito@quinnemanuel.com>; Eric Stops <ericstops@quinnemanuel.com>; Evangeline Shih <evangelineshih@quinnemanuel.com>; Andrew Chalson <andrewchalson@quinnemanuel.com>; AJones@durietangri.com; Frank Calvosa <frankcalvosa@quinnemanuel.com>; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel <jazzavadel@quinnemanuel.com>; DSilver@McCarter.com; Alex.Grabowski@lw.com; jazzpatentlitigation.lwteam@lw.com
Subject: RE: Jazz v. Avadel, No. 21-691

[EXTERNAL EMAIL from audra.sawyer@lw.com]

Gabe,

Avadel is considering your proposed schedules for an expedited appeal and an emergency motion to stay at the Federal Circuit. So that we can better understand Jazz's positions, we believe the parties should meet and confer today. Please be prepared to address why Jazz believes an emergency motion to the Federal Circuit is appropriate given that Jazz did not ask the district court for expedited briefing of its stay motion or propose a schedule for briefing of that motion to Avadel and further given Judge Williams' Order requiring Avadel to file its opposition on Thursday December 1, and Avadel's subsequent offer to file its opposition on Tuesday November 29.

Best,

Audra

From: Gabriel Brier <gabrielbrier@quinnemanuel.com>
Sent: Sunday, November 27, 2022 1:23 PM
To: Yue, Herman (NY) <Herman.Yue@lw.com>
Cc: Schuler, Kenneth (CH) <KENNETH.SCHULER@lw.com>; Zubick, Marc (CH/NY) <Marc.Zubick@lw.com>; Wang, Sarah (CH) <Sarah.Wang@lw.com>; Ning, Sunnie (BN) <Sunnie.Ning@lw.com>; Propst, Sarah (DC) <Sarah.Propst@lw.com>; DDurie@durietangri.com; KDavis@durietangri.com; ajoyce@mccarter.com; Nick Cerrito <nickcerrito@quinnemanuel.com>; Eric Stops <ericstops@quinnemanuel.com>; Evangeline Shih <evangelineshih@quinnemanuel.com>; Andrew Chalson <andrewchalson@quinnemanuel.com>; AJones@durietangri.com; Frank Calvosa <frankcalvosa@quinnemanuel.com>; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel <jazzavadel@quinnemanuel.com>; Sawyer, Audra (DC) <Audra.Sawyer@lw.com>; DSilver@McCarter.com; Grabowski, Alex (CH) <Alex.Grabowski@lw.com>; #C-M JAZZ PATENT LITIGATION - LW TEAM <jazzpatentlitigation.lwteam@lw.com>
Subject: Jazz v. Avadel, No. 21-691

Counsel,

As we have previously informed you, Jazz intends to file a motion for an expedited appeal of the Court's delisting order with the Federal Circuit. Please let us know as soon as possible whether Avadel will oppose Jazz's motion to expedite or file a response.

If Avadel does not oppose Jazz's motion to expedite, please let us know whether Avadel agrees to the following expedited schedule for briefing and consideration of the merits of Jazz's appeal:

- Jazz's opening brief: December 16, 2022
- Avadel's response brief: January 13, 2023
- Jazz's reply brief: January 20, 2023
- Oral argument: during the Court's February session.

Jazz also intends to seek an emergency motion to stay the District Court's order at the Federal Circuit if the District Court does not act on Jazz's request for a stay by tomorrow afternoon. Given Avadel's letter to the District Court last week, we assume Avadel will oppose the motion, but please let us know if that is correct and, if so, whether Avadel intends to file a response. To the extent that Avadel intends to file a response, we propose the following expedited briefing schedule for the motion to stay:

- Jazz's opening brief: November 28, 2022
- Avadel's response: November 30, 2022
- Any reply by Jazz: December 1, 2022.

Please let us know as soon as possible whether Avadel agrees to this briefing schedule for the motion to stay.

Regards,

Gabe

Gabe Brier | **quinn emanuel urquhart & sullivan, llp**
51 Madison Avenue, 22nd Floor, New York, NY 10010 | Office: (212) 849-7000 | Direct: (212) 849-7486 | Mobile: (917) 576-3454 | Fax: (212) 849-7100 | gabrielbrier@quinnemanuel.com

EXHIBIT B

From:	Gabriel Brier
To:	Yue, Herman (NY)
Cc:	Schuler, Kenneth (CH); Zubick, Marc (CH/NY); Wang, Sarah (CH); Ning, Sunnie (BN); Propst, Sarah (DC); DDurie@durietangri.com; KDavis@durietangri.com; ajoyce@mccarter.com; Nick Cerrito; Eric Stops; Evangeline Shih; Andrew Chalson; AJones@durietangri.com; Frank Calvosa; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel; Sawyer, Audra (DC); DSilver@McCarter.com; Grabowski, Alex (CH); #C-M JAZZ PATENT LITIGATION - LW TEAM
Subject:	Jazz v. Avadel, Nos. 21-691, 21-1138, 21-1594
Date:	Tuesday, November 22, 2022 7:06:27 AM

Counsel,

Jazz will shortly be filing an expedited appeal of the Court's delisting order and Jazz intends to seek a stay of the Court's delisting order pending Jazz's expedited appeal. Please confirm by 2:00 pm Eastern whether Avadel will consent to Jazz's request for a stay. We are available today to meet and confer if you would like to discuss.

Regards,

Gabe

Gabe Brier | quinn emanuel urquhart & sullivan, llp
51 Madison Avenue, 22nd Floor, New York, NY 10010 | Office: (212) 849-7000 | Direct: (212) 849-7486 | Mobile: (917) 576-3454 | Fax: (212) 849-7100 | gabrielbrier@quinnemanuel.com

EXHIBIT C

No. 23-1186

United States Court of Appeals for the Federal Circuit

JAZZ PHARMACEUTICALS, INC.,

Plaintiff-Appellant,

v.

AVADEL CNS PHARMACEUTICALS, LLC,

Defendant-Appellee.

Appeal from the United States District Court for the District of Delaware, in No. 1:21-cv-00691-GBW, Judge Gregory Brian Williams

DECLARATION OF KIRA A. DAVIS IN SUPPORT OF APPELLEE'S OPPOSITION TO EXPEDITING CONSIDERATION OF APPELLANT'S MOTION TO STAY PENDING APPEAL

I, Kira A. Davis, do hereby state and declare as follows:

1. I am an attorney in the law firm Durie Tangri LLP and one of the attorneys representing Defendant-Appellee Avadel CNS Pharmaceuticals, LLC ("Avadel") in the district court proceedings underlying this appeal.

2. I make this declaration in support of Avadel's Opposition to Expediting Consideration of Appellant's Motion to Stay Pending Appeal.

3. On Tuesday, November 22, 2022, we received an email from counsel for Plaintiff-Appellant Jazz Pharmaceuticals, Inc. ("Jazz") that (a) notified Avadel that Jazz intended to file a motion for a stay of the district court's November 18, 2022 delisting order pending Jazz's appeal thereof and (b) offered to meet and confer. We accepted the offer of a meet and confer, and met by telephone that same day.

4. On that call, Jazz did not propose a schedule for its district court motion to stay pending appeal. I asked counsel for Jazz what schedule they were proposing. Counsel for Jazz referenced the Local Rules schedules. In the District of Delaware, the Local Rules provide for 14 days for an opposition brief to be filed—i.e., December 6.

Executed on: November 29, 2022

/s/ Kira A. Davis (with permission)
Kira A. Davis

EXHIBIT D

From: Gabriel Brier
To: Yue, Herman (NY)
Cc: Schuler, Kenneth (CH); Zubick, Marc (CH/NY); Wang, Sarah (CH); Ning, Sunnie (BN); Propst, Sarah (DC); DDurie@durietangri.com; KDavis@durietangri.com; ajoyce@mccarter.com; Nick Cerrito; Eric Stops; Evangeline Shih; Andrew Chalson; AJones@durietangri.com; Frank Calvosa; JBlumenfeld@morrisnichols.com; JTigan@morrisnichols.com; JazzAvadel; Sawyer, Audra (DC); DSilver@McCarter.com; Grabowski, Alex (CH); #C-M JAZZ PATENT LITIGATION - LW TEAM
Subject: Jazz v. Avadel, No. 21-691
Date: Sunday, November 27, 2022 10:23:29 AM

Counsel,

As we have previously informed you, Jazz intends to file a motion for an expedited appeal of the Court's delisting order with the Federal Circuit. Please let us know as soon as possible whether Avadel will oppose Jazz's motion to expedite or file a response.

If Avadel does not oppose Jazz's motion to expedite, please let us know whether Avadel agrees to the following expedited schedule for briefing and consideration of the merits of Jazz's appeal:

- Jazz's opening brief: December 16, 2022
- Avadel's response brief: January 13, 2023
- Jazz's reply brief: January 20, 2023
- Oral argument: during the Court's February session.

Jazz also intends to seek an emergency motion to stay the District Court's order at the Federal Circuit if the District Court does not act on Jazz's request for a stay by tomorrow afternoon. Given Avadel's letter to the District Court last week, we assume Avadel will oppose the motion, but please let us know if that is correct and, if so, whether Avadel intends to file a response. To the extent that Avadel intends to file a response, we propose the following expedited briefing schedule for the motion to stay:

- Jazz's opening brief: November 28, 2022
- Avadel's response: November 30, 2022
- Any reply by Jazz: December 1, 2022.

Please let us know as soon as possible whether Avadel agrees to this briefing schedule for the motion to stay.

Regards,

Gabe

Gabe Brier | quinn emanuel urquhart & sullivan, llp
51 Madison Avenue, 22nd Floor, New York, NY 10010 | Office: (212) 849-7000 | Direct: (212) 849-7486 | Mobile: (917) 576-3454 | Fax: (212) 849-7100 | gabrielbrier@quinnemanuel.com

EXHIBIT E

From: ded_nefreply@ded.uscourts.gov
To: ded_ecf@ded.uscourts.gov
Subject: Activity in Case 1:21-cv-00691-GBW Jazz Pharmaceuticals, Inc. v. Avadel CNS Pharmaceuticals, LLC Motion to Stay
Date: Tuesday, November 22, 2022 3:24:01 PM

This is an automatic e-mail message generated by the CM/ECF system. Please DO NOT RESPOND to this e-mail because the mail box is unattended.
*****NOTE TO PUBLIC ACCESS USERS*** Judicial Conference of the United States policy permits attorneys of record and parties in a case (including pro se litigants) to receive one free electronic copy of all documents filed electronically, if receipt is required by law or directed by the filer. PACER access fees apply to all other users. To avoid later charges, download a copy of each document during this first viewing. However, if the referenced document is a transcript, the free copy and 30 page limit do not apply.**

U.S. District Court

District of Delaware

Notice of Electronic Filing

The following transaction was entered by Tigan, Jeremy on 11/22/2022 at 6:23 PM EST and filed on 11/22/2022

Case Name: Jazz Pharmaceuticals, Inc. v. Avadel CNS Pharmaceuticals, LLC
Case Number: 1:21-cv-00691-GBW
Filer: Jazz Pharmaceuticals, Inc.
Document Number: 235

Docket Text:
MOTION to Stay re [232] Order,, -- *Motion to Stay Pending Appeal or, in the Alternative, a Stay Pending Application to the Federal Circuit for a Stay Pending Appeal* -- - filed by Jazz Pharmaceuticals, Inc.. (Tigan, Jeremy)

1:21-cv-00691-GBW Notice has been electronically mailed to:

Alan Devlin alan.devlin@lw.com

Alex M. Grabowski alex.grabowski@lw.com

Alexandra M. Joyce ajoyce@mccarter.com, amiller@mccarter.com, mhitchens@mccarter.com

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1:21-cv-00691-GBW Filer will deliver document by other means to:

Bornali R. Borah
UNDELIVERABLE EMAIL 11/3/2022

The following document(s) are associated with this transaction:

Document description: Main Document
Original filename:n/a
Electronic document Stamp:
[STAMP dcecfStamp_ID=1079733196 [Date=11/22/2022] [FileNumber=5051075-0] [ae9fa2916b542291e77ecbef390d697da1ea4e71bc79123ddc28c13a59adb4f6a4790bbad397b70bd5d733ca91fc5d6204112424b88122904c62079d4d0959dc]]

EXHIBIT F

Report to Congress

The Listing of Patent Information in the Orange Book

Submitted Under Section 2(e) of the
Orange Book Transparency Act of 2020

Executive Summary

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (Hatch-Waxman Amendments). The Hatch-Waxman Amendments require the U.S. Food and Drug Administration (FDA or Agency) to, among other things, make publicly available, with monthly supplements, a list of approved drug products. FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* publication (commonly known as the Orange Book) and this publication's monthly Cumulative Supplements satisfy this requirement. The Orange Book identifies drug products approved by FDA under section 505(c) and 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The *Addendum* to the Orange Book identifies drugs that have qualified under the FD&C Act for periods of exclusivity and provides patent information concerning certain approved drug products listed in the Orange Book.

The FD&C Act requires new drug application (NDA) applicants[1] to file with their application "the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that" (1) "claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent" or (2) "claims a method of using such drug for which approval is sought or has been granted in the application" (section 505(b)(1)(A)(viii) of the FD&C Act (21 U.S.C. 355(b)(1)(A)(viii)); see also 21 CFR 314.53). After approval of an NDA (including certain types of supplements to an NDA) but within certain time frames prescribed in the FD&C Act and FDA's implementing regulations, NDA holders[2] must submit required patent information for listing in the Orange Book (see section 505(c)(2) of the FD&C Act and 21 CFR 314.53). The FD&C Act requires FDA to regularly revise the Orange Book to include, among other things, patent information submitted under section 505(c)(2) of the FD&C Act (see section 505(j)(7)(A)(iii) of the FD&C Act). FDA serves a ministerial role with regard to the listing of patent information.

Both (1) an NDA submitted pursuant to section 505(b)(2) of the FD&C Act (a 505(b)(2) application) that relies, at least in part, on FDA's finding of safety and/or effectiveness for a listed drug and (2) an abbreviated new drug application (ANDA) must include an appropriate patent certification or statement for each patent that claims either the listed drug(s) relied upon or the reference listed drug (RLD), respectively, or a method of using such listed drug and for which information is required to be filed under section 505(b) or 505(c) of the FD&C Act. The timing of approval for a 505(b)(2) application and an ANDA (including a petitioned ANDA[3]) is subject to certain patent and exclusivity protections.

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[1] An *NDA applicant* is any person who submits an NDA to obtain FDA's approval of a new drug.
[2] An *NDA holder* is the applicant that owns an approved NDA.
[3] A *petitioned ANDA* is a type of ANDA for a drug product that differs from the RLD in its dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which FDA has determined, in response to a petition submitted under section 505(j)(2)(C) of the FD&C Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product. A petitioned ANDA is generally expected to provide the same therapeutic effect as the listed drug that was relied on as the basis of the suitability petition.

On January 5, 2021, the President signed into law the Orange Book Transparency Act (OBTA) of 2020 (Pub. L. 116-290). Section 2(e) of the OBTA requires the Agency (1) to solicit public comments regarding the types of patent information that should be included in, or removed from, the Orange Book and (2) to transmit to Congress, by January 5, 2022, a summary of the comments received and any actions the Agency is considering taking in response to these comments. This report to Congress fulfills both requirements of section 2(e) of the OBTA.

Prior to the enactment of the OBTA, FDA had solicited comments—through a *Federal Register* public docket established on June 1, 2020—on patent listing issues.[4] FDA reopened that docket on October 16, 2020, and again, after enactment of the OBTA, on March 16, 2021. FDA received 24 comments, preceding and subsequent to the enactment of the OBTA, in response to the public docket regarding the listing of patent information in the Orange Book. Each comment contained input on one or more issues related to the listing of patent information in the Orange Book. The comments expressed a variety of different and sometimes competing views on the types of patents and other information that should be included in, or removed from, the Orange Book.

In response to these public comments, FDA will create a multidisciplinary working group within the Agency. This working group will evaluate whether additional clarity is needed regarding the types of patents, patent information, or other patent-related information that should be included in, or removed from, the Orange Book, consistent with the current statutory requirements for patent listing in the FD&C Act. Additionally, as part of an Agency-wide effort to modernize the Orange Book, improve transparency, and provide useful information to regulated industry and the public, FDA will consider, in evaluating whether further improvements to the Orange Book should be made, the comments that provided additional insight into how stakeholders and the public have been utilizing the Orange Book.

The OBTA requires that the Government Accountability Office submit a related report to Congress not later than 2 years after enactment of the OBTA that may help inform the Agency's thinking on a number of these issues and, as such, FDA will review this report once it is available.

[4] See "Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments" (85 FR 33169, Docket No. FDA-2020-N-1127 (June 1, 2020)).

Table of Contents

I. Introduction

On January 5, 2021, the President signed into law the Orange Book Transparency Act (OBTA) of 2020 (Pub. L. 116-290).

The OBTA amends section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and, among other things, (1) revises the requirements for submission of patent information by new drug application (NDA) applicants[5] and (2) by clarifying the types of patent and exclusivity-related information to be listed in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* publication (commonly known as the Orange Book or "the list"), including when certain patent information must be removed from the Orange Book. These revisions were generally consistent with existing regulations and practices of the U.S. Food and Drug Administration (FDA or Agency).

Section 2(e) of the OBTA requires that,

> *[n]ot later than 1 year after the date of enactment of this Act, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall—*
>
> *(1) solicit public comment regarding the types of patent information that should be included on, or removed from, the list under section 507(j)(7) of the [FD&C] Act (21 U.S.C. 355(j)(7)); and*
>
> *(2) transmit to Congress a summary of such comments and actions [FDA] is considering taking, if any, in response to public comment pursuant to paragraph (1) about the types of patent information that should be included or removed from such list.*

Prior to the enactment of the OBTA, FDA had solicited comments—through a public docket established on June 1, 2020—on patent listing issues.[6] FDA reopened that docket on October 16, 2020, and again, after enactment of the OBTA, on March 16, 2021. In total, FDA received 24 comments in response to this public docket. Each comment contained input on one or more issues related to the listing of patent information in the Orange Book. The comments expressed a variety of different and sometimes competing views on the types of patents and other information that should be included in, or removed from, the Orange Book.

In response to the directive in section 2(e) of the OBTA, FDA prepared the following report summarizing the public comments received regarding the types of patent information that should be included in, or removed from, the Orange Book under section 507(j)(7) of the FD&C Act. In

[5] An *NDA applicant* is any person who submits an NDA to obtain FDA's approval of a new drug.
[6] See "Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments" (85 FR 33169, Docket No. FDA-2020-N-1127 (June 1, 2020)).

addition, this report summarizes the actions FDA is considering taking in response to these public comments.

Additionally, section 2(f) of the OBTA requires that the Government Accountability Office (GAO) submit a report to Congress, as follows:

> *(1) IN GENERAL.—Not later than 2 years after the date of enactment of this Act, the Comptroller General of the United States (referred to in this section as the ''Comptroller General'') shall submit to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives a report on the patents included in the list published under section 505(j)(7) of the [FD&C] Act (21 U.S.C. 355(j)(7)) that claim an active ingredient or formulation of a drug in combination with a device that is used for delivery of such drug, including an analysis of such patents and their claims.*
>
> *(2) CONTENT.—The Comptroller General shall include in the report under paragraph (1)—*
>
> > *(A) data on— (i) the number of patents included in the list published under section 505(j)(7) of the [FD&C] Act (21 U.S.C. 355(j)(7)) that claim the active ingredient or formulation of a drug in combination with a device that is used for delivery of the drug, and that together claim the finished dosage form of the drug; and (ii) the number of claims with respect to each patent included in the list published under such section 505(j)(7) that claim a device that is used for the delivery of the drug, but do not claim such device in combination with an active ingredient or formulation of a drug;*
> >
> > *(B) an analysis of the listing of patents described in subparagraph (A)(ii), including the timing of listing such patents in relation to patents described in subparagraph (A)(i), and the effect listing the patents described in subparagraph (A)(ii) has on market entry of one or more drugs approved under section 505(j) of the [FD&C] Act as compared to the effect of not listing the patents described in subparagraph (A)(ii); and*
> >
> > *(C) recommendations about which kinds of patents relating to devices described in subparagraph (A)(i) should be submitted to the Secretary of Health and Human Services for inclusion on the list under section 505(j)(7) of the [FD&C] Act and which patents should not be required to be so submitted in order to reduce barriers to approval and market entry.*

II. Background

A. The Orange Book

On May 31, 1978, in response to requests from state health agencies for FDA's assistance in administering their laws relating to the substitution of drug products, the Commissioner of Food and Drugs sent a letter to officials of each state announcing FDA's intent to provide not only a list of all prescription drug products that had been approved for safety and effectiveness by FDA but also therapeutic equivalence (TE)[7] determinations for multisource prescription products. This list was distributed to the public as a proposal in January 1979 (see 44 FR 2932 (January 12, 1979)). This proposed list, which later became known as the Orange Book, included only prescription drug products that had been approved by FDA and were marketed at the time of publication. On October 31, 1980, FDA published a final version of the list (45 FR 72582), which was the first Orange Book.

On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417) (Hatch-Waxman Amendments). The Hatch-Waxman Amendments require FDA to, among other things, make publicly available, with monthly supplements, a list of approved drug products. The Orange Book and its monthly Cumulative Supplements satisfy this requirement.

The Orange Book identifies drug products approved by FDA under section 505(c) and 505(j) of the FD&C Act. The main criterion for the inclusion of a product in the Orange Book is that it has an NDA or abbreviated new drug application (ANDA) that has been approved and that has not been withdrawn for safety or effectiveness reasons or determined by FDA to have been withdrawn for safety or effectiveness reasons.

1. Composition of the Orange Book

The Orange Book is composed of the following four main parts:

(1) The Prescription Drug Product List, which is a list of approved marketed prescription drug products with therapeutic equivalence evaluations (which, along with the OTC Drug Product List that is also in the Orange Book, is referred to as the "Active Section");

(2) The OTC Drug Product List, which is a list of marketed over-the-counter (OTC) drug products that have been approved in NDAs or ANDAs (which, along with the Prescription Drug Product List, is referred to as the "Active Section");

[7] Approved drug products are *therapeutic equivalents* if they are pharmaceutical equivalents for which bioequivalence has been demonstrated and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling (21 CFR 314.3(b)).

(3) The Drug Products with Approval under Section 505 of the FD&C Act Administered by the Center for Biologics Evaluation and Research List; and

(4) The Discontinued Drug Product List (commonly referred to as the "Discontinued Section"), which is a cumulative list of approved drug products that have never been marketed, are for exportation (e.g., only marketed outside the United States), are for military use, are not commercially distributed by a U.S. federal or state governmental entity, have been discontinued from marketing and FDA has not determined that they were withdrawn from sale for reasons of safety or effectiveness, or have had their approvals withdrawn for reasons other than safety or effectiveness subsequent to being discontinued from marketing.

The Orange Book contains additional information, including in three appendices and an addendum related to patents and exclusivity. In particular, the *Addendum* to the Orange Book identifies drugs that have qualified under the FD&C Act for periods of exclusivity and provides patent information concerning certain approved drug products listed in the Orange Book. The Orange Book website also has a number of additional resources that can assist stakeholders with using the Orange Book and answer related questions.[8]

In addition, the Orange Book contains TE evaluations for approved multisource prescription drug products, which are reflected, for drug products, in the Active Section. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education on drug product selection and to foster containment of healthcare costs.[9]

2. Submission and Listing of Patent Information

The FD&C Act has established requirements for FDA, NDA applicants, and NDA holders[10] related to the submission of patent information and the listing of patent information in the Orange Book. The FD&C Act requires NDA applicants to file with their application "the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that" (1) "claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent" or (2) "claims a method of using such drug for which approval is sought or has been granted in the application" (see section 505(b)(1)(A)(viii) of the FD&C Act; see also 21 CFR 314.53). An NDA applicant is required to amend its application to include this information if a patent that claims such drug or a method of using such drug is issued

[8] The Orange Book home page is available at https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm.

[9] TE evaluations in the Orange Book are not official FDA actions affecting the legal status of products under the FD&C Act. See, e.g., 45 FR 72582 at 72597 (October 31, 1980). Drug products with approved applications that are *single-source* (i.e., there is only one approved product available for that active ingredient, dosage form, route of administration, and strength) are also included in the Orange Book, but no TE code is included with such products.

[10] An *NDA holder* is the applicant that owns an approved NDA.

after the filing date but before approval of the application" (section 505(b)(1)(b) of the FD&C Act (21 U.S.C. 355(b)(1)(A)(viii)); see also 21 CFR 314.53). After approval of an NDA (including certain types of supplements to an NDA) but within certain time frames prescribed in the FD&C Act and FDA's implementing regulations, NDA holders must submit the required information on any patent that meets the criteria for submission with an application, except that a patent claiming a method of using such drug may only be submitted if it claims a use approved in the NDA. Also, an NDA holder is required to submit information on certain patents that are issued after its application is approved (see section 505(c)(2) of the FD&C Act and 21 CFR 314.53). The FD&C Act requires FDA to regularly revise the Orange Book to include, among other things, patent information submitted under section 505(c)(2) of the FD&C Act (see section 505(j)(7) of the FD&C Act). FDA serves a ministerial role with regard to the listing of patent information (see, e.g., "Applications for FDA Approval to Market a New Drug: Patent Submission and Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not be Infringed" final rule, 68 FR 36676 at 36683 (June 18, 2003) ("Indeed, the requirement of prompt publication ("upon submission"), combined with the 30-day time frame for updating the Orange Book, are strong evidence that Congress did not intend us to undertake anything other than a ministerial action.")).

3. Facilitate Implementation of the Hatch-Waxman Amendments

Since enactment of the Hatch-Waxman Amendments, FDA has provided recommendations and issued regulations pertaining to the patent listing requirements of the FD&C Act to facilitate implementation of these amendments. Below is a brief summary of those efforts.

a. Letters to Industry

FDA has provided NDA applicants and NDA holders with advice on how to comply with certain requirements, including the new requirements for submission of patent information, via letters to industry. These letters have demonstrated how FDA's thinking on the appropriateness of the listing of certain patents has evolved. For example, shortly after enactment of the Hatch-Waxman Amendments, the Agency indicated that formulation patents were not covered by the FD&C Act and therefore should not be submitted for listing in the Orange Book. However, in 1985, FDA reconsidered its original position and stated that it intended to list composition patents, including formulation patents, claiming the drug for which the NDA was submitted and for which a claim of patent infringement could reasonably be asserted in the event of unlicensed manufacture, use, or sale of the drug.

b. Rulemakings

In 1989, FDA issued a proposed rule to implement the Hatch-Waxman Amendments, detailing the types of patents that FDA regarded as covered by the requirements in section 505(b)(1) and 505(c)(2) of the FD&C Act. In particular, FDA proposed that to comply with section 505(b)(1) and 505(c)(2) of the FD&C Act, NDA applicants would be required to submit information on drug (ingredient) patents, drug product (formulation and composition) patents, and method-of-

use patents (see "Abbreviated New Drug Application Regulations" proposed rule, 54 FR 28872 at 28918 (July 10, 1989)). The proposed rule excluded process patents from the types of patents required to be submitted. When FDA issued a final rule in 1992, FDA declined to finalize patent listing and certain other requirements and stated that because the Agency would be issuing final regulations governing patent certification and exclusivity at a future date, FDA was revising or deleting cross-references to those provisions and, when possible, replacing them with statutory citations (see "Abbreviated New Drug Application Regulations" final rule, 57 FR 17950 at 17951 (April 28, 1992)).

In 1994, FDA finalized the regulations governing certain patent and exclusivity provisions of the Hatch-Waxman Amendments, including patent listing requirements (see "Abbreviated New Drug Application Regulations; Patent and Exclusivity Provisions" final rule, 59 FR 50338 (October 3, 1994)). In response to a comment suggesting that clarification was needed on whether patent information on manufacturing processes is appropriate for submission to FDA, the preamble to the final rule reiterated that the regulation at 21 CFR 314.53(b) clearly states that information on process patents should not be submitted to FDA (59 FR 50338 at 50345 (October 3, 1994)).

In 2002, FDA issued a proposed rule in response to (1) disputes over whether certain listed patents met the regulatory requirements for listing in the Orange Book and (2) a request from the Federal Trade Commission to issue a regulation or guidance clarifying whether an NDA holder can list various types of patents in the Orange Book (see "Applications for FDA Approval to Market a New Drug: Patent Listing Requirements and Application of 30-Month Stays on Approval of Abbreviated New Drug Applications Certifying That a Patent Claiming a Drug Is Invalid or Will Not be Infringed" proposed rule, 67 FR 65448 at 65449 (October 24, 2002)). The proposed rule addressed (1) the types of patents that must and must not be listed, including, among others, certain patents that claim methods of use; (2) the patent certification statement that NDA applicants must submit as part of an NDA or a supplement to an NDA; and (3) the 30-month stay of approval for a 505(b)(2) application or an ANDA set out in the Hatch-Waxman Amendments (see also section 505(c)(3)(C) and 505(j)(5)(B)(iii) of the FD&C Act). In addition to proposing to clarify that NDA holders and NDA applicants must not submit information on patents that claim methods of use that are not approved for the listed drug or are not the subject of the pending application, respectively, the proposed regulation at 21 CFR 314.53(a) proposed to prohibit the listing of information on patents claiming packaging, patents claiming metabolites, and patents claiming intermediates (67 FR 65448 at 65451 (October 24, 2002)). The proposed rule, however, proposed to require NDA applicants and NDA holders to submit information on product-by-process patents (i.e., patents that claim a product by using or listing process steps to wholly or partially define the claimed product) and patents that claimed a drug substance even when the patented drug substance was a different form than the drug substance that was the subject of the pending or approved NDA as long as the drug substances were the same (67 FR 65448 at 65452 (October 24, 2002)).

FDA issued the final rule on patent listing requirements, with certain revisions, on June 18, 2003. The final rule revised FDA's regulations to (1) incorporate the proposals described above with certain revisions; (2) prohibit the submission of patents claiming packaging, intermediates, or

metabolites; (3) require the submission of certain patents claiming a different polymorphic form of the active ingredient described in the NDA; and (4) add a requirement that for submission of polymorph patents, the NDA holder must have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA (see 68 FR 36676 at 36677 (June 18, 2003)).[11] The preamble to the final rule addressed comments on the types of patents that must and must not be submitted, including comments stating that patents claiming devices or containers that are either "integral" to the drug product or require prior FDA approval should be submitted and listed (68 FR 36676 at 36680). The comments described a distinction between packaging and devices such as metered dose inhalers and transdermal patches, which are drug delivery systems used and approved in combination with a drug. In response to the comment, FDA (1) agreed that patents claiming a package or container must not be submitted and (2) clarified that such packaging and containers are distinct from the drug product and thus fall outside of the requirements for patent submission (68 FR 36676 at 36680 (June 18, 2003)). FDA did not expressly address device-related patents associated with NDAs but clarified the rule to require submission of patents that claim the drug product as defined in FDA's regulation at 21 CFR 314.3(b), which defines a *drug product* as "a finished dosage form, e.g., tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients." FDA explained that the "key factor" in determining whether the patent must or must not be submitted for listing is whether the patent claims the finished dosage form of the approved drug product. Patents must not be submitted for bottles or containers and other packaging, as these are not "dosage forms" (68 FR 36676 at 36680 (June 18, 2003)).

In 2015, FDA proposed regulations to implement portions of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) (Pub. L. 108-173), which amended provisions of the FD&C Act that govern the approval of 505(b)(2) applications and ANDAs (MMA proposed rule) ("Abbreviated New Drug Applications and 505(b)(2) Applications" proposed rule, 80 FR 6802 (February 6, 2015)). Also in the MMA proposed rule, FDA recommended to amend certain regulations, including regulations regarding the submission of patent information, to facilitate the compliance with and efficient enforcement of the FD&C Act.

The MMA final rule, which was issued in 2016, among other actions, revised and streamlined the requirements for submission of patent information on (1) patents that claim the drug substance and/or drug product and meet the requirements for patent listing on that basis, (2) drug substance patents that claim only a polymorph of the active ingredient, and (3) certain NDA supplements ("Abbreviated New Drug Applications and 505(b)(2) Applications" final rule, 81 FR 69580 (October 6, 2016)). For example, in the MMA final rule, FDA clarified that an applicant need only satisfy the requirements for patent listing set forth in section 505(b)(1) and 505(c)(2) of the FD&C Act and, subject to the requirements for the submission of method-of-use

[11] The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Pub. L. 108-173) superseded certain provisions of the 2003 final rule related to 30-month stays of approval; these superseded provisions were subsequently revoked by a technical amendment (see "Application of 30-Month Stays on Approval of ANDAs and Certain NDAs Containing a Certification That a Patent Claiming the Drug Is Invalid or Will Not Be Infringed" technical amendment (69 FR 11309 (March 10, 2004))).

patent information, need not identify each basis on which the patent claims the drug (see 81 FR 69580 at 69596 (October 6, 2016). Accordingly, if a patent is eligible for listing as claiming both the drug substance and the drug product, an applicant would only be required to identify one of these two bases for listing (see 21 CFR 314.53(c)(2)(i)(S) and 314.53(c)(2)(ii)(T)). In addition, this MMA final rule codified FDA's longstanding position that the NDA holder's description of the patented method of use required for publication must contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method-of-use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval (see 21 CFR 314.53(c)(2)(ii)(P)(*3*)). For example, the rule requires that if the method(s) of use claimed by the patent does not cover an indication or other approved condition of use in its entirety, then the applicant must describe only the specific approved method of use claimed by the patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product (see 21 CFR 314.53(c)(2)(ii)(P)(*3*)).

B. Patent Certifications and Exclusivities – Timing of Approval of 505(b)(2) Applications and ANDAs

The timing of approval for a 505(b)(2) application and an ANDA (including a petitioned ANDA[12]) is subject to certain patent and exclusivity protections.

A 505(b)(2) application and ANDA must include an appropriate patent certification or statement for each patent that claims the listed drug(s) relied upon or the reference listed drug (RLD), respectively, or a method of using such drug and for which information is required to be filed under section 505(b) or 505(c) of the FD&C Act. The 505(b)(2) or ANDA applicant must submit one or more of the following certifications or statements:

- That such patent information has not been filed (a paragraph I certification);
- That such patent has expired (a paragraph II certification);
- The date on which such patent will expire (a paragraph III certification);
- That such patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the 505(b)(2) application or ANDA is submitted (a paragraph IV certification);

[12] A *petitioned ANDA* is a type of ANDA for a drug product that differs from the the reference listed drug in its dosage form, route of administration, strength, or active ingredient (in a product with more than one active ingredient) and for which FDA has determined, in response to a petition submitted under section 505(j)(2)(C) of the FD&C Act (suitability petition), that studies are not necessary to establish the safety and effectiveness of the proposed drug product. A petitioned ANDA is generally expected to provide the same therapeutic effect as the listed drug that was relied on as the basis of the suitability petition.

- That there are no patents that claim the listed drug(s) or that claim a use of such drug (a "no relevant patents" statement, which is submitted instead of a patent certification); or

- That a method-of-use patent does not claim a use for which the 505(b)(2) or ANDA applicant is seeking approval (a 505(b)(2)(B) or 505(j)(2)(A)(viii) statement).

An applicant that submits a paragraph IV certification is required to give notice of the paragraph IV certification to the NDA holder for the listed drug(s) relied upon or RLD and to each owner of the patent that is the subject of the certification. Notice of a paragraph IV certification subjects the 505(b)(2) or ANDA applicant to the risk that it will be sued for patent infringement. If the NDA holder or patent owner initiates a patent infringement action within 45 days after receiving notice of the paragraph IV certification, there generally will be a statutory 30-month stay of approval of the 505(b)(2) application or ANDA while the patent infringement litigation is pending (see section 505(c)(3)(C) and 505(j)(5)(B)(iii) of the FD&C Act).

If a patent is timely listed in the Orange Book after a 505(b)(2) application or ANDA is submitted but before it is approved, the applicant generally must amend its application and provide an appropriate patent certification or statement to the newly listed patent, but a 30-month stay of approval will not be available (see section 505(c)(3)(C) and 505(j)(5)(B)(iii) of the FD&C Act).

C. Risk Evaluation and Mitigation Strategies

The Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85) created section 505–1 of the FD&C Act (21 U.S.C. 355–1), which authorizes FDA to require a risk evaluation and mitigation strategy (REMS) if FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. A *REMS* is a required risk management strategy that employs tools beyond prescribing information to ensure that the benefits of a drug outweigh its risks. A REMS may require inclusion of a Medication Guide and/or a patient package insert to provide risk information to patients (see section 505–1(e)(2) of the FD&C Act) and/or a communication plan to disseminate risk information to healthcare providers (see section 505–1(e)(3) of the FD&C Act). A REMS may also include certain packaging and disposal requirements under section 505-1(e)(4) of the FD&C Act. In addition, FDA may require certain elements to assure safe use (ETASU) when such elements are necessary to mitigate specific serious risks associated with a drug (see section 505–1(f) of the FD&C Act). ETASU may include, for example, requirements that healthcare providers who prescribe the drug have particular training or experience, that patients using the drug be monitored, or that the drug be dispensed to patients with evidence or other documentation of safe-use conditions. When a REMS with ETASU is required for the RLD, section 505–1(i)(1)(C) of the FD&C Act, as amended by the Further Consolidated Appropriations Act, 2020 (Pub. L. 116-94), requires that the holder of an ANDA approved under section 505(j) of the FD&C Act use either a "single, shared system"' with the RLD holder for the ETASU or a "different, comparable aspect" of the ETASU. FDA is aware that some NDA holders have obtained patents claiming the way one or more of their REMS requirements have been implemented and that this can impact the ability of

a prospective generic applicant to form a single, shared system with the NDA holder. The prospect of NDA holders obtaining patents for REMS was also contemplated by Congress in the FDAAA, which, prior to the amendments made to section 505–1 of the FD&C Act by the Further Consolidated Appropriations Act, 2020, (1) required the RLD and ANDA holders to use a single, shared system for the ETASU unless FDA waived the requirement and (2) provided that one of the grounds for which FDA could waive the single, shared system requirement would be if an aspect of the ETASU was claimed by a patent and the ANDA applicant certified that it sought a license to that aspect and was unable to obtain one (see 21 U.S.C. 355–1(i)(1)(B)(ii), 2012 ed.). FDA notes that section 505–1(f)(8) of the FD&C Act provides that no holder of an approved covered application shall use any ETASU to block or delay the approval of an application under section 505(b)(2) or 505(j) of the FD&C Act or to prevent application of such element to a drug that is the subject of an ANDA.

D. FDA's Solicitation of Public Comments Regarding Patent Listing in the Orange Book

Prior to the enactment of the OBTA, FDA published, on June 1, 2020, a *Federal Register* notice entitled "Listing of Patent Information in the Orange Book; Establishment of a Public Docket; Request for Comments" (85 FR 33169, Docket No. FDA-2020-N-1127). This notice announced the establishment of a public docket and solicited comments on not only the types of patents currently listed in the Orange Book but also the impact that any change to current patent listing practices may have on drug product development. Comments were due by August 31, 2020. The notice included questions related to the following five topics: (1) general questions, (2) drug product patents, (3) method-of-use patents, (4) REMS-related patents, and (5) patents for digital applications. The Agency received 16 comment letters in response to this solicitation.

This docket was reopened for a second comment period from October 16 to November 16, 2020. The Agency received four comment letters in response to this second solicitation.

Section 2(e) of the OBTA, which the President signed into law on January 5, 2021, requires the Agency (1) to solicit public comments regarding the types of patent information that should be included in, or removed from, the Orange Book and (2) to transmit to Congress, by January 5, 2022, a summary of the comments received and any actions the Agency is considering taking in response to these comments.

To ensure that commenters had an opportunity to consider patent listing issues in light of the OBTA, FDA reopened the comment period for the public docket for a third time for a period of 30 days—from March 16 to April 15, 2021—to allow interested persons time to submit any additional comments regarding the types of patent information that should be included in, or removed from, the Orange Book. The Agency received four comments in response to this third solicitation.

This report to Congress includes a summary of the 24 comments FDA received in the public docket, preceding and subsequent to the enactment of the OBTA (i.e., on June 1, 2020, and

reopened on October 16, 2020, and March 16, 2021), regarding the types of patent information that should be included in, or removed from, the Orange Book.

III. Summary of the Public Docket Comments Received

As mentioned above, FDA received 24 comments in the *Federal Register* public docket; each comment contained input on one or more patent issues. FDA received comments from academia, pharmaceutical industry associations, brand and generic drug manufacturers, biopharmaceutical research companies, consulting firms, law firms, intellectual property and drug pricing advocacy groups, biotechnology and trade organizations, information services companies, a pharmacist, and a patient. Several comments included general remarks regarding FDA's authority and involvement with patents and exclusivities without focusing on particular patent information that should be included in, or removed from, the Orange Book.

In sections IIIA through IIIE of this report, the specific comments received are organized under the following five categories: (1) general questions, (2) drug product patents, (3) method-of-use patents, (4) REMS-related patents, and (5) patents for digital applications; these categories are based on the questions posed in FDA's June 1, 2020, *Federal Register* notice that first established the public docket.

The below summary of the comments received is not intended to express a view on these comments, including whether such comments accurately described current statutory or regulatory requirements. In addition, FDA received off-topic comments on issues expressing political views; those comments are not summarized here as they are not relevant to the types of patent information that should be included in, or removed from, the Orange Book.

The public docket comments, which are listed based on the particular *Federal Register* solicitation in which they were received, are available at the following websites:

- First solicitation (June 1, 2020): https://www.regulations.gov/document/FDA-2020-N-1127-0001/comment
- Second solicitation (October 16, 2020): https://www.regulations.gov/document/FDA-2020-N-1127-0019/comment
- Third solicitation (March 16, 2021): https://www.regulations.gov/document/FDA-2020-N-1127-0024/comment

A. General Questions

Comments in this category responded to the following five questions:

1. Do 505(b)(2) and ANDA applicants currently encounter any challenges because certain types or categories of patents are not listed in FDA's Orange Book?

2. Given the general increasing complexity of products approved in an NDA (e.g., drug-device combination products, complex delivery systems, associated digital applications), are there any aspects of FDA's interpretation of the statutory requirement for NDA holders to submit information on a patent that claims the drug or a method of using such drug that are not sufficiently clear? If there is a lack of clarity, how could this be resolved?

3. How would NDA holders and prospective 505(b)(2) and ANDA applicants weigh any advantages that may result from listing of additional types or categories of patent in the Orange Book against the potential need to submit additional patent certifications that could result in a delay of approval of a 505(b)(2) application or ANDA?

4. If you think FDA should clarify the type of patents that must be listed in the Orange Book, what factors should FDA consider in implementing this clarification? For example, should FDA consider specific factors in evaluating the timeliness of patent information submitted after such clarification?

5. Are there other issues related to the listing of patent information that we should consider?

The comments received in response to this first general set of questions covered a range of topics, and commenters also expressed a range of perspectives on these topics. For example, a variety of comments provide input on (1) whether the current requirements related to the listing of patent information in the Orange Book should be clarified or modified and (2) on the types of patents commenters considered appropriate for listing or the benefits or drawbacks of different patent listing approaches. One comment appears to support the current listing requirements and indicates that FDA should not create additional types or categories of patents eligible to be listed in the Orange Book.

Another comment generally supports the listing of any patent that claims an FDA-approved drug product, which the comment asserts includes the product's integrated and essential constituent parts, and suggests that both NDA holders and prospective applicants for follow-on products (including products submitted in ANDAs and 505(b)(2) applications) would benefit from an inclusive patent listing framework that enables orderly pre-launch litigation regarding the validity, enforceability, or applicability of any patent that might delay or otherwise inhibit the prompt entry of FDA-approved follow-on drug products.

However, another comment appears to support a more restrictive patent listing framework, stating that the Orange Book was originally developed to list drug patents and contending that expansion to include medical device and digital application patents, among other patents, deviates substantially from one of the Orange Book's central premises: to establish clearly

defined bounds of market exclusivity, further generic competition, and lower prices. Another comment states that, consistent with the holding and reasoning of the First Circuit in *In re: Lantus Direct Purchaser Antitrust Litig.*, 284 F.Supp.3d 91 (1st Cir. 2018), FDA should prohibit device and component patents from being listed in FDA's Orange Book and only list drug and method-of-use patents. Another comment suggests patents other than those which claim the drug or an approved method of using the drug are currently listed in the Orange Book and recommends that FDA delist most secondary and all tertiary patents from the Orange Book, especially those patents that do not "claim the drug" or "methods of using the drug."

One comment contends that allowing companies to include additional patents in the Orange Book would extend their monopoly over critical drugs.

Other comments propose various modifications to the current listing requirements that could change the categories of patents listed and either limit or expand the number of patents listed. For example, one comment recommends more limited listing requirements, proposing that only patents protecting innovations that improve health and have been demonstrated to do so through clinical testing should be rewarded with the benefits of "patent linkage." The comment suggests that this proposal would be achieved by creating a new field in the Orange Book to distinguish health-contributing patents (which would enjoy added protection through "patent linkage") from non-contributing patents (which would not).

Another comment suggests that if FDA considered an extra component (e.g., an electronic device) in making a TE determination, the patent information listed in the Orange Book should include the relevant patents—including software, device, drug, or any other patents—that claim the drug with the component considered for the TE determination. Another comment notes the uncertainty and potential that digital health technologies hold and indicates that future therapeutics will continue to integrate features and technologies that are complex and not contemplated by traditional features limited solely to active ingredients, formulations, and methods of use; the comment therefore urges the continued evaluation of the Orange Book's (1) practices in this area and (2) policies that encourage disclosure of patent information, as the commenter believes such disclosure better serves all relevant stakeholders and encourages industry competition.

One commenter had not encountered any problems regarding certain types or categories of patents not being listed in the Orange Book. However, another comment notes challenges with NDA holders bringing litigation against 505(b)(2) and ANDA applicants with regard to patents that have not been listed in the Orange Book. That commenter specifically notes that litigation for non-Orange Book-listed patents can occur at a different time than the litigation contemplated under the Hatch-Waxman Amendments for Orange Book-listed patents and can lead to delayed launches of substitutable generics. This same commenter, though, states that there has been an increase in the listing of ineligible patents in the Orange Book and notes that this adds unnecessary costs and barriers to the approval of generic competitors.

Some comments address whether aspects of FDA's interpretation of the statutory or regulatory requirements related to patent listing are sufficiently clear. One comment suggests that there are

aspects of FDA's statutory interpretations regarding the types of patents for complex products that are and are not subject to listing in the Orange Book that would benefit from greater clarity. Another comment states that the rules for patents claiming drug-device combination products are not clear and suggests, to avoid errors or abuse, implementing a referee process by which FDA enforces the rules about which patents must be listed. Another comment states that FDA should clarify that patents that claim a device or component of a device that are encompassed within (i.e., part of) an NDA-approved drug-device combination product are required to be listed, including patents with claims covering an entire delivery device or a component part of a delivery device that are encompassed within the NDA. Another comment asserts that recent litigation on "skinny labels"[13] suggests that courts are willing to place undue emphasis on method-of-use patents (citing *GlaxoSmithKline LLC v. Teva Pharmaceuticals USA, Inc.*[14]) and then suggests that FDA should take a position in the Orange Book on the assertability of certain method-of-use patents against ANDAs with "skinny labels."

Another comment suggests that, given the general increasing complexity of products approved in NDAs, there is a lack of clarity with respect to FDA's practices for listing certain products in the Orange Book and for making therapeutic equivalence evaluations for these products. In addition, this comment suggests (1) that the Orange Book should list products with components such as a sensor, electronic device, or digital application separately from the drug product alone if there is a difference in clinical outcome associated with the additional component and (2) that FDA should provide clarity on its criteria for making TE evaluations for products with components like these relative to the drug product without such a component.

Other comments discuss the timelines for implementing any clarification to the types of patents that must be listed in the Orange Book. One comment indicates that if FDA does clarify that additional types of patents must be listed in the Orange Book, this clarification should allow applicants a sufficient time period to file a supplemental listing request. Two comments similarly suggest that if FDA seeks to clarify its regulatory requirements in future rulemaking proceedings, any new patent listing rules should apply only prospectively. Another comment states that FDA should provide a time frame for listing patents that are only listed due to new clarifications consistent with its timely listing requirement, i.e., within 30 days of the effective date of the clarification. The same comment states that for patents already listed that would be delisted following clarification, the patent listing dispute process could be sufficiently used and, for patents not currently listed that would become eligible for listing after clarification, a window of not more than 180 days during which patents already issued as of the date of clarification may be listed.

Several comments provide input on what information is disclosed in the Orange Book about listed patents and other subjects and offer various views on what additional information either should be made available by FDA or should be required to be disclosed by the holders of the listed drugs. For example, one comment suggests that FDA should identify which patents are late-listed. Another comment suggests adding the following fields to the Orange Book:

[13] The commenter describes a "skinny label" as ANDA labeling that intentionally excludes patented indications.
[14] 976 F.3d 1347 (Fed. Cir. 2020). The Federal Circuit has since withdrawn this opinion and issued a new panel opinion on August 5, 2021. See 7 F.4th 1320 (Fed. Cir. 2021).

paragraph IV information, National Drug Code (NDC) information, Drugs@FDA information, submission dates for original applications, 505(b)(2) designations, orphan drug information, and descriptions of exclusivity and patent codes. Relatedly, another comment suggests that when an ANDA containing a paragraph IV certification is received, FDA should notate the NDA Orange Book listing to identify the NDA and strength for which the ANDA was submitted. Additionally, the commenter recommends that FDA identify the parts of the NDA labeling that are protected by method-of-use patents listed in the Orange Book to make labeling carve-outs easier for ANDA applicants. Another comment suggests that for each product protected by patents or a regulatory exclusivity, FDA should require applicants to provide periodic information about the number of units sold and the sales revenue.

One comment suggests that FDA should publish the number of patents ever listed for a specific product in the searchable electronic Orange Book database, including patents that have expired and have been delisted from the current edition. Another comment suggests that FDA should either (1) retain a list of expired patents in the Orange Book but clearly state that these patents have expired or (2) periodically publish a separate list with every patent ever listed in the Orange Book (including those that have expired); further, this comment indicates this list should be made available in a database that can be searchable by end-users and also in data files with an open format.

One comment suggests that FDA should add information about government disclosures on patents listed in the Orange Book and opines that the ideal approach would be to include this information in the list of data items that NDA applicants or NDA holders are required to provide under 21 CFR 314.50(h), 314.53, and 314.70(f). Another comment suggests that FDA should require disclosures about previous and current litigation, if any, for each patent listed in the Orange Book, including all legal events concerning each patent (e.g., disputes over infringement and validity, failure to disclose government rights as required under 35 U.S.C. 202(c)(6) and 37 CFR 1.77(b)(3), pending and past march-in requests, 28 U.S.C. 1498 cases, or inter partes' reviews at the United States Patent and Trademark Office).

A few comments asked for more Orange Book-related information to be made available for research purposes. One comment suggests that FDA should publish Orange Book data files with dates that would allow researchers to estimate the number of years a specific drug has been or will be under some form of exclusivity; this suggestion is aimed at furthering research regarding secondary patenting and helping answer questions relating to, for example, how long a drug is typically under some form of exclusivity or whether the trend has been changing recently. Another comment suggests that the forms that contain required patent information submitted to FDA by NDA applicants (i.e., Forms FDA 3542 and FDA 3542a) should be published on FDA's website, alongside existing Orange Book information, so that patent researchers can make use of the data more easily, more quickly understand the scope of patent protection on specific drugs, and more efficiently perform research on broader trends in pharmaceutical patenting.

FDA also received a few comments regarding other topics, including the forms used to submit patent information to FDA and the format used to display information in the electronic version of

the Orange Book. One comment contends that Form FDA 3542 and the usage of this form discourages the complete identification of patent information required by the statute and suggests that Form FDA 3542 may be improved in several ways to facilitate proper patent listing in the Orange Book.

B. Drug Product Patents

Comments in this category responded to the following two questions:

1. Are there elements of FDA's regulatory definition of drug product or dosage form in 21 CFR 314.3(b) that may be helpful to clarify to assist NDA holders in determining whether a patent claims the finished dosage form of an approved drug product?

2. What factors should FDA consider in providing any clarifications related to whether device-related patents need to be submitted for listing as a patent that claims the drug? For example, what are the advantages and disadvantages of requiring patents that claim a device constituent part of a combination product approved under section 505 of the FD&C Act to also claim and/or disclose the active ingredient or formulation of the approved drug product (or the drug product class) to fall within the type of patent information that is required to be submitted to FDA for listing in the Orange Book? Also, how, if at all, should this analysis be affected by considerations about whether the device or specific component of device claimed in the patent is "integral" (see 68 FR 36676 at 36680) to the administration of the drug?

In response to the first question, one comment generally suggests that FDA should clarify its interpretation of its 21 CFR 314.3(b) "drug product" and "dosage form" definitions as they relate to the listing of device patents. Another comment suggests that FDA should clarify the definitions for drug-device combination products, especially those with primarily a container-closure function, with a clarification as to which features of such devices are eligible for patent claims to be listed in the Orange Book.

Other comments provide input about whether device-related patents should be submitted for listing as a patent that claims the drug and whether FDA should consider clarifying this topic. One comment states that FDA should construe "patent which claims the drug" to mean any patent that (1) claims one or more articles used as a component of the drug product or (2) claims the composition of the drug product (e.g., a combination of such components or specific amounts, ratios, or configurations thereof).

One comment contends that patents should be listed in the Orange Book so long as (1) the patent at issue legitimately claims an integrated device component of an approved NDA product or a method of using such a constituent part and (2) FDA directly reviewed that integrated device component in connection with, and as a condition of approving, the listed NDA product.

Another comment suggests that all patents that (1) claim an integrated device component of an approved NDA product (or a method of using such an integrated device component) and (2) have the potential to block the marketing of an approved follow-on product should be listed in the Orange Book.

Multiple comments provide input on whether patents that claim a device constituent part of a combination product approved in an NDA should also be required to claim or disclose the active ingredient or formulation of the drug to be listed in the Orange Book. A number of these comments suggest that such patents should not be required to claim or disclose the active ingredient to be listed. For example, two comments suggest that FDA should clarify that a patent that claims a device or device component need not also claim or expressly call out the active ingredient in the drug to be considered a patent that "claims the drug" under section 505(b)(1) of the FD&C Act. One comment states that FDA should confirm that patents claiming the device constituent part of an NDA-approved drug-device combination product or a component thereof, including patents that do not disclose or claim the active ingredient or formulation of the approved drug product, meet the listing standard. A similar comment states that FDA should not construe section 505(b)(1) of the FD&C Act in a manner that limits the listing of patents that claim a device constituent part of a combination product only to those patents that expressly claim or recite a device or device component in combination with the drug's active ingredient or formulation. Two comments suggest that FDA should define what constitutes a drug delivery system and make clear that patents that claim pre-filled drug delivery devices should be listed if the approved product is a drug-device combination product that encompasses that device, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.

One comment suggests (1) that while claiming the drug active ingredient should be sufficient to render a patent that claims a device or device component subject to listing, this claim should not be construed as a necessary factor and (2) that when a patent that claims a device or device component does not claim the device or device component in combination with the drug's active ingredient, determining whether that patent is subject to listing should turn on whether the device as used with the drug product meets the Agency's regulatory definition of a *combination product* as set forth at 21 CFR 3.2(e), even if the drug product is not specifically designated as such by FDA.

However, another comment suggests that a patent should claim either the "drug product" or "dosage form" of an NDA product for it to be listed in the Orange Book and not simply claim an element in the drug product or dosage form, e.g., a delivery device or packaging element. This comment requests that FDA clarify that listed patents need to include claims to the active ingredient in the drug product.

A few comments provide input on how the analysis of whether device-related patents should be submitted for listing could be affected by considerations about whether the device or specific component of the device claimed in the patent is "integral." One comment suggests that defining "integral" would help clarify whether a patent should be listed or not and argues that if a patent claim covers any part of an NDA-approved drug product or the method of using that product that is "integral" to the approved product, then that patent should be listed. Two comments indicate

that FDA should accept device patents for listing in the Orange Book but only if the device constituent part of a drug product claimed in the patent is integral to the drug's delivery system and is reviewed and approved as part of the NDA; one of these commenters notes that this requirement not only limits the eligibility to patents that meet the applicable statutory and regulatory requirements but also reduces the potential for anti-competitive "game-playing" by brand companies.

C. Method-of-Use Patents

Comments in this category responded to the following three questions:

1. What information should FDA consider regarding when a patent that claims a method of using a device constituent part, or only a component of a device constituent part, might or might not meet the statutory standard for submission by the NDA holder for listing in the Orange Book as a method-of-use patent? Should FDA consider whether: (1) The patent claims and/or discloses the active ingredient or formulation of the approved drug product (or the drug product class)?; (2) the device constituent part is described in certain sections of the listed drug labeling?; or (3) use of the device is described in labeling for the listed drug, but the device is not a constituent part of the drug product? Should FDA consider whether the drug product labeling states that the drug is only for use with the specific device? Should FDA also consider device labeling, for example whether the device labeling indicates the device is for use with the specific drug?

2. What information should FDA consider regarding whether there are circumstances in which a patent claiming the way an approved drug product is administered would meet the statutory standard for submission by the NDA holder for listing in the Orange Book as a drug product patent rather than a method-of-use patent?

3. What information should FDA consider regarding whether there are circumstances in which a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book?

A number of comments provide information that the commenters think FDA should consider regarding circumstances in which method-of-use patents that claim a method of using a device constituent part or a component of a device constituent part might or might not meet the standard for listing in the Orange Book. For example, one comment states that FDA should only permit method-of-use device patents to be listed if they claim an active ingredient of a drug product or the drug product itself. Another comment similarly indicates that these patents should be listed in the Orange Book if they claim an active ingredient of a drug product or the drug product itself and notes that the labeling of the drug should substantiate that the device is an integral part of the dosage form.

Another comment indicates that FDA should consider whether the patent claims cover the specific active pharmaceutical ingredient (API), API class, or formulation of the relevant drug product. The same comment said that patents claiming a method of using a device constituent part should only be listed if the claims present a novel "use case" (i.e., use of the drug with the patented device constituent part should be a different "use case" than use of the drug with a non-patented version of that device constituent part for the patent to be listed). The comment also states that a method-of-use patent should only be listed if the device is critical to the administration of the drug for a method of use described in the Indications section of the drug product's labeling. Also, this comment notes that when use of the device is described in labeling for the listed drug but the device is not a constituent part of the drug product, listing of a patent related to a method-of-use for the device should only be considered if the drug product is also specifically referenced in the device labeling.

One comment suggests FDA should consider whether there is a difference in clinical outcomes in determining whether method-of-use patents that claim a method of using a device constituent part or a component of a device constituent part might meet the statutory standard for listing.

However, two comments interpret the FD&C Act and FDA's implementing regulations to require listing of patents claiming a method of using a device constituent part or component thereof in an NDA-approved single-entity combination product if the patent could reasonably be asserted upon an unlicensed person engaging in the manufacture, use, or sale of the drug—regardless of whether the patent claims and/or discloses the active ingredient or formulation of the approved drug product (or the drug product class). Another comment indicates that a patent claiming a method of using a pre-filled drug delivery device or a component thereof (e.g., a patent claiming a method for determining the final dose of a drug contained in a cartridge in a pen-type injector through the configuration or operation of certain device components) should be subject to the patent listing requirement, even if the patent does not claim or disclose the active ingredient, formulation, or finished dosage form.

FDA also received input about the information the Agency should consider regarding whether there are circumstances in which a patent claiming the way an approved drug product is administered would meet the statutory standard for submission for listing as a drug product patent rather than a method-of-use patent. One comment states that when determining whether to list a patent as a drug patent or a method-of-use patent, FDA should consider whether the method of administration for the drug could make a clinical difference to all patients or to a defined subgroup of patients sufficient to be identified in the drug's label. Another comment contends that FDA should be guided by how an applicant characterizes the patent in its Form FDA 3542 and suggests that if the Form FDA 3542 indicates that the patent claims one or more approved methods of using the drug product, the patent would qualify as a method-of-use patent, whereas if the Form FDA 3542 indicates that the patent claims an active ingredient or the approved drug product, the patent would qualify as a drug substance or a drug product patent, respectively.

In addition, some comments provide input in response to the second question about what

information FDA should consider regarding whether there are circumstances in which a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book.[15] Several comments argue against listing method-of-use patents for a method of administration that is not described in approved product labeling. One comment contends that a method-of-use patent that claims the way a drug product is administered that is not described in the FDA-approved product labeling should not be included in the Orange Book because this type of patent is of a more general nature and not specific to the drug product or dosage form. Another comment states that patents covering methods of administration not related to a drug's indication should not be listed in the Orange Book because otherwise, an ANDA applicant would be forced to certify to patents on methods of use for which they are not seeking approval. Similarly, another comment argues that since the mode of delivery is part of the "Prescribing Information" of the labeling, if the way an approved drug product is administered is not referenced in the FDA-approved product labeling, then the way that the drug product is administered is not a part of the approved drug product and listing of the patent is not proper in this context. Another comment states that it would not be appropriate to authorize the listing of method-of-use patents that do not claim FDA-approved methods of administering a listed drug product and indicates that doing so would be impossible to square with the text and structure of the Hatch-Waxman Amendments and FDA's implementing regulations.

However, one comment contends that the NDA applicant, not FDA, must assess whether a method-of-use patent claiming the way an approved drug product is administered that is not described in FDA-approved product labeling would meet the statutory standard for listing in the Orange Book. Another comment notes that FDA's role in patent listing matters is purely ministerial and, accordingly, the statute and its corresponding regulations should govern in this and all circumstances.

D. REMS-Related Patents

Comments in this category responded to the following two questions:

1. What information should FDA consider regarding whether patents that claim how the sponsor has implemented a particular REMS requirement meet the statutory requirement for the type of patent information that is required to be submitted to FDA for listing in the Orange Book? What factors should be considered in making this determination?

2. Are there other issues related to patents that claim how the sponsor has implemented a particular REMS requirement that FDA should consider with regard to listing patent information in the Orange Book, including any potential

[15] Certain comments were submitted to this docket before enactment of the OBTA. The OBTA amended section 505(c)(2) of the FD&C Act to state, in part: "a patent that is identified as claiming a method of using such drug shall be filed only if the patent claims a method of use approved in the application."

> impact listing such patents in the Orange Book could have on development of REMS for generic versions of products? For example, does listing patent information in the Orange Book for such patents pose difficulties for ANDA applicants in developing a single, shared system REMS for that product?

As with the preceding categories, the comments received in this category reflected a range of different and sometimes competing views.

Some comments provide circumstances in which the commenters believe REMS-related patents should be listed in the Orange Book. For example, one comment indicates that REMS patents should be listed in the Orange Book as long as a claim of patent infringement could reasonably be asserted. Another comment states that patents are not, and should not be, excluded from eligibility for listing in the Orange Book solely on the ground that they relate to a REMS because the statute does not exclude patents otherwise meeting the listing criteria from listing based on the subject matter to which they relate. Another comment contends that the statute and corresponding regulations already identify the factors that govern whether a REMS-related patent must be listed and, because FDA has a ministerial role with respect to patent listing, states that the Agency should not develop an alternative framework beyond what is in the statute.

In contrast, multiple comments contend that REMS-related patents should not be listed in the Orange Book. One comment states that REMS requirements frequently concern such topics as the distribution of drug products or enhanced monitoring of adverse events and do not meet the statutory requirement for the type of patents that should be listed in the Orange Book. Similarly, another comment indicates that REMS are meant to provide additional safety measures to permit a drug to be marketed when the drug is associated with risks or adverse events to be managed and that REMS-related patents are not similar to categories of patents listable in the Orange Book. Another comment indicates that, given the well-documented history of brand application holders' misuse of the REMS requirements for anticompetitive purposes, there is a concern that REMS-related patents, if listed, would be particularly subject to abuse. The comment states that FDA should not list patents that claim one or more elements of a REMS because such patents do not claim the relevant drug or a method of using such drug. More generally, one comment suggests that REMS and patents should be handled separately and argues that REMS are for safety and patent listings are for critical patents that need to be challenged or expire before ANDA marketing. One comment suggests that FDA should delist REMS patents from the Orange Book and clarify that such patents should not be invoked as a roadblock to generic approval or market entry of important pharmaceutical products.

Other comments express views about the potential impact listing such patents in the Orange Book could have on the development of REMS for generic versions of products or on the approval of generic drugs. For example, one comment argues that listing REMS patents creates difficulties for ANDA applicants to develop a single, shared REMS with the RLD's NDA holder for that product because that NDA holder would likely claim that the ANDA applicant would need to obtain patent licenses as part of the discussion for that single, shared REMS. However, another comment contends that, in light of the enactment of the Further Consolidated Appropriations Act, 2020, any concerns regarding the impact of patent listing on the

development of REMS for generic versions of products are unfounded.

One comment contends that REMS innovation does not benefit patients or advance clinical care, and another comment indicates that listing REMS-related patents would harm competition and undermine the FDAAA, as REMS should not be used to block or delay a generic application. Similarly, another comment states that section 505-1(f)(8) of the FD&C Act mandates that holders of approved applications must not use any ETASU to block or delay approval of another application, and this comment also indicates that listing of patents pertaining to REMS with ETASU represents a barrier to approval that runs counter to this goal of the legislation. Another comment states that it would be a serious mistake to allow companies to file REMS-related patents in the Orange Book, which would result in 30-month stays of approval for ANDAs and provide NDA holders opportunities to improperly delay the entry of competition.

Other comments suggest areas for clarification by FDA regarding REMS-related patents. One comment suggests that FDA should clarify whether it considers "patents claiming safe methods of patient treatment or administration (e.g., marker-assisted methods for adjusting and administering drug doses)" to be patents that claim a REMS. Another comment states that FDA should clarify what it considers to be a patent that claims how an application holder has implemented a REMS and whether a patent should be listed should depend on whether the patent is deemed to claim "the drug" or "a method of using the drug," not on special rules or prohibitions that hinge on whether a REMS is implemented or not.

Finally, one comment suggests that FDA should be listed as co-inventors on certain REMS patents as a condition of approval, thereby allowing FDA to "license" the REMS patent to any and all ANDA applicants.

E. Patents for Digital Applications

Comments in this category responded to the following two questions:

1. If an approved drug product has an associated digital application (e.g., a mobile application that accepts and records information from an ingestible sensor in a drug product), what factors should be considered in determining whether a patent that claims an aspect of that digital application meets the standards for listing in the Orange Book?

2. Are there other issues related to patents for digital applications associated with approved drugs that should be considered with regard to listing patent information in the Orange Book?

FDA received a number of comments providing a range of views regarding the factors that should be considered in determining whether a patent that claims an aspect of a digital application associated with an approved drug product meets the standards for listing in the Orange Book.

One comment suggests listing patents only to the extent they claim integrated device constituent parts that FDA has expressly reviewed and approved as a condition of approval of the NDA, but further suggests such patents should not be listed to the extent they cover separable prescription drug-use-related software that is not accompanied by safety or efficacy claims. Another comment suggests listing patents for digital applications in the Orange Book under the following three specific scenarios: (1) when the mobile application is considered a medical device and the mobile application plays a critical role in the safety or efficacy of the product when administered for an approved indication; (2) when the functionality of the application could pose a risk to a patient's safety if the device were to not function as intended; and (3) when the application provides a patient-specific analysis, a patient-specific diagnosis, or treatment recommendations. Another comment contends that when a digital application (1) serves only to help patients self manage a disease or a condition without a specific treatment suggestion or (2) automates simple tasks for healthcare providers, patents for the application should not be listed in the Orange Book.

One comment states that if a patent claims a method of using an approved drug product in combination with an associated digital application, and this digital application is referenced in the approved drug labeling, then the patent should be listed in the Orange Book as long as a claim of patent infringement could reasonably be asserted.

One comment suggests that determining whether a patent that claims a digital application associated with an approved drug product should be subject to listing should turn on whether the patent for the digital application meets the statutory standard of claiming the drug or a method of using the drug; this comment also suggests that FDA should consider convening public workshops or meetings at which questions in this area could be discussed.

Another comment indicates that it is not possible to identify all the factors and issues the Agency should consider when determining whether patents on digital applications should be listed in the Orange Book at this time, given the nascent status of digital technologies, but suggests that patents claiming a digital application be listed in the Orange Book either when the digital application is approved as part of a combination product with the drug under an NDA or when the software is referenced by name in the drug labeling.

Commenters also raise other issues related to patents for digital applications and listing information about these patents and the associated approved drugs in the Orange Book. For example, one comment contends that patents on digital tools should not be listed in the Orange Book as a means of preventing generic entry of compounds that contain the same small molecule ingredient, asserting as an example, "a new 'digital' version of the blockbuster drug Abilify (aripiprazole) which includes an ingestible sensor, a smartphone application, and a wearable sensor." The commenter asserts that patents on these components should not be assertable against generic "non-digital" versions of the product.

Another comment suggests that FDA should create a separate section in the Orange Book for approvals that include digital applications and argues that failure to create this separation would

undercut the incentives created by Orange Book listing and lead to confusion at the pharmacy level that may allow pharmacists to substitute basic drug product formulations for products with smart components.

Two comments suggest that the Orange Book should reflect that approved smart products (which include the drug product formulation and smart components) are not therapeutically equivalent to non-digitally enhanced products that have the same drug product formulation (e.g., use a bioequivalent capsule or tablet).

IV. The Actions FDA Is Considering in Response to the Public Comments

This section of the report provides information on the actions the Agency is considering taking in response to the public comments summarized above.

The Agency convened a working group in order to review the comments received and prepare this report. As noted in section III of this report, the comments received provided a variety of different and sometimes competing views on the types of patent information that should be included in, or removed from, the Orange Book. The diversity of viewpoints on these topics indicate a need to examine these issues more closely and suggests that there is not a consensus view around specifc proposed changes that should be made to the types of patent information included in the Orange Book; rather, the comments suggested that there are a variety of equities and issues to be considered in examining this topic and that some of these issues are still evolving.

In response to the public comments summarized above, FDA will build upon the efforts of the working group that reviewed the comments and will create a multidisciplinary working group within the Agency to evaluate whether additional clarity is needed regarding the types of patent information that should be included on, or removed from, the Orange Book, consistent with the existing statutory requirements for patent listing in the FD&C Act.

In performing this evaluation, the Agency will consider the amendments to the FD&C Act included in the OBTA, the diversity of perspectives presented by stakeholders, and the Agency's ministerial role with respect to the listing of patent information. In considering what steps may be appropriate to take to provide additional clarity on the types of patent information that should be included in, or removed from, the Orange Book, FDA will also consider the comments received regarding factors FDA should consider in implementing any clarification.

Additionally, as part of an Agency-wide effort to modernize the Orange Book, improve transparency, and provide useful information to regulated industry and the public, FDA will consider the comments that provided additional insight into how stakeholders and the public have utilized the Orange Book and whether further improvements to the Orange Book should be made, including improvements that are not related to the types of patent information included in the Orange Book. Further, the Agency will continue to consider the more general comments received to the public docket that suggest modifications to the Orange Book beyond the types of

patent information that should be included in, or removed from, the Orange Book as part of this ongoing effort.

Lastly, FDA notes that the GAO report required to be completed within 2 years after the date of enactment of the OBTA may help inform the Agency's thinking on a number of these issues; as such, the GAO report will be reviewed by FDA once it is available.

V. Conclusion

- On January 5, 2021, the President signed into law the OBTA of 2020 (Pub. L. 116-290). Section 2(e) of the OBTA, in part, requires the Agency to solicit public comments regarding the types of patent information that should be included in, or removed from, the Orange Book. In response to this directive, FDA solicited public comments and received 24 comment letters in response to the public docket, each containing input on one or more issues related to the listing of patent information in the Orange Book.

- In response to the public comments, FDA will create a multidisciplinary working group within the Agency to evaluate, based on its review of the comments and changes to the statute in the OBTA, whether additional clarity is needed regarding the types of patent information that should be included in, or removed from, the Orange Book, consistent with the existing statutory requirements for patent listing in the FD&C Act.

EXHIBIT G

116TH CONGRESS, 1st Session } HOUSE OF REPRESENTATIVES { REPORT 116–47

ORANGE BOOK TRANSPARENCY ACT OF 2019

MAY 2, 2019.—Committed to the Committee of the Whole House on the State of the Union and ordered to be printed

Mr. PALLONE, from the Committee on Energy and Commerce, submitted the following

R E P O R T

[To accompany H.R. 1503]

[Including cost estimate of the Congressional Budget Office]

The Committee on Energy and Commerce, to whom was referred the bill (H.R. 1503) to amend the Federal Food, Drug, and Cosmetic Act regarding the list under section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act, and for other purposes, having considered the same, report favorably thereon with an amendment and recommend that the bill as amended do pass.

CONTENTS

The amendment is as follows:

Strike all after the enacting clause and insert the following:

SECTION 1. SHORT TITLE.

This Act may be cited as the "Orange Book Transparency Act of 2019".

SEC. 2. ORANGE BOOK.

(a) SUBMISSION OF PATENT INFORMATION FOR BRAND NAME DRUGS.—Paragraph (1) of section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) is amended to read as follows:

"(b)(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application—

"(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use;

"(B) a full list of the articles used as components of such drug;

"(C) a full statement of the composition of such drug;

"(D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

"(E) such samples of such drug and of the articles used as components thereof as the Secretary may require;

"(F) specimens of the labeling proposed to be used for such drug;

"(G) any assessments required under section 505B; and

"(H) patent information, with respect to each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug, and consistent with the following requirements:

"(i) The applicant shall file with the application the patent number and the expiration date of—

"(I) any patent which claims the drug for which the applicant submitted the application and is a drug substance (including active ingredient) patent or a drug product (including formulation and composition) patent; and

"(II) any patent which claims the method of using such drug.

"(ii) If an application is filed under this subsection for a drug and a patent of the type described in clause (i) which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include such patent information.

Upon approval of the application, the Secretary shall publish the information submitted under subparagraph (H). The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by subparagraph (A).".

(b) CONFORMING CHANGES TO REQUIREMENTS FOR SUBSEQUENT SUBMISSION OF PATENT INFORMATION.—Section 505(c)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)) is amended—

(1) by inserting after "the patent number and the expiration date of any patent which" the following: "fulfills the criteria in subsection (b) and";

(2) by inserting after the first sentence the following: "Patent information that is not the type of patent information required by subsection (b) shall not be submitted."; and

(3) by inserting after "could not file patent information under subsection (b) because no patent" the following: "of the type required to be submitted in subsection (b)".

(c) LISTING OF EXCLUSIVITIES.—Subparagraph (A) of section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)) is amended by adding at the end the following:

"(iv) For each drug included on the list, the Secretary shall specify each exclusivity period that is applicable and has not concluded under—

"(I) clause (ii), (iii), or (iv) of subsection (c)(3)(E) of this section;

"(II) clause (iv) or (v) of paragraph (5)(B) of this subsection;

"(III) clause (ii), (iii), or (iv) of paragraph (5)(F) of this subsection;

"(IV) section 505A;

"(V) section 505E; or

"(VI) section 527(a).".

(d) REMOVAL OF INVALID PATENTS.—

(1) IN GENERAL.—Section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)) is amended by adding at the end the following:

"(D)(i) The holder of an application approved under subsection (c) for a drug on the list shall notify within 14 days the Secretary in writing if either of the following occurs:

"(I) The Patent Trial and Appeals Board issues a decision from which no appeal has been or can be taken that a patent for such drug is invalid.

"(II) A court issues a decision from which no appeal has been or can be taken that a patent for such drug is invalid.

"(ii) The holder of an approved application shall include in any notification under clause (i) a copy of the decision described in subclause (I) or (II) of clause (i).

"(iii) The Secretary shall remove from the list any patent that is determined to be invalid in a decision described in subclause (I) or (II) of clause (i)—

"(I) promptly; but

"(II) not before the expiration of any 180-day exclusivity period under paragraph (5)(B)(iv) that relies on a certification described in paragraph (2)(A)(vii)(IV) that such patent was invalid.".

(2) APPLICABILITY.—Subparagraph (D) of section 505(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)), as added by paragraph (1), applies only with respect to a decision described in such subparagraph that is issued on or after the date of enactment of this Act.

(e) REVIEW AND REPORT.—Not later than one year after the date of enactment of this Act, the Secretary of Health and Human Services, acting through the Commissioner of Food and Drugs, shall—

(1) solicit public comment regarding the types of patent information that should be included on the list under section 507(j)(7) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)(7)); and

(2) transmit to the Congress an evaluation of such comments, including any recommendations about the types of patent information that should be included on or removed from such list.

SEC. 3. GAO REPORT TO CONGRESS.

(a) IN GENERAL.—Not later than one year after the date of enactment of this Act, the Comptroller General of the United States (referred to in this section as the "Comptroller General") shall submit to the Committee on Energy and Commerce of the House of Representatives a report on the patents included in the list published under section 505(j)(7) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(j)(7)), including an analysis and evaluation of the types of patents included in such list and the claims such patents make about the products they claim.

(b) CONTENTS.—The Comptroller General shall include in the report under subsection (a)—

(1) data on the number of—

(A) patents included in the list published under paragraph (7) of section 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355(j)), that claim the active ingredient or formulation of a drug in combination with a device that is used for delivery of the drug, together comprising the finished dosage form of the drug; and

(B) claims in each patent that claim a device that is used for the delivery of the drug, but do not claim such device in combination with an active ingredient or formulation of a drug;

(2) data on the date of inclusion in the list under paragraph (7) of such section 505(j) for all patents under such list, as compared to patents that claim a method of using the drug in combination with a device;

(3) an analysis regarding the impact of including on the list under paragraph (7) of such section 505(j) certain types of patent information for drug product applicants and approved application holders, including an analysis of whether—

(A) the listing of the patents described in paragraph (1)(A) delayed the market entry of one or more drugs approved under such section 505(j); and

(B) not listing the patents described in paragraph (1)(A) would delay the market entry of one or more such drugs; and

(4) recommendations about which kinds of patents relating to devices described in paragraph (1)(A) should be submitted to the Secretary of Health and Human Services for inclusion on the list under paragraph (7) of such section 505(j) and which patents should not be required to be so submitted.

PURPOSE AND SUMMARY

H.R. 1503, the "Orange Book Transparency Act of 2019", was introduced on March 5, 2019, by Rep. Kelly (D–IL), and referred to the Committee on Energy and Commerce. H.R. 1503 would require manufacturers to share complete and timely patent information with the Food and Drug Administration (FDA), ensure that periods of exclusivity listed in the Orange Book are promptly updated, and

clarify that patents found to be invalid through a court decision or a decision by the Patent Trial and Appeal Board would be required to be removed from the Orange Book promptly, but not before time for appeal has expired. The bill would also direct the U.S. General Accountability Office (GAO) to study which types of patents should be listed in the Orange Book.

BACKGROUND AND NEED FOR LEGISLATION

Approved branded and generic drug products currently marketed are included on a list commonly referred to as the "Orange Book," [1] which is published on the FDA's website and includes, among other details, the patents that protect each product, the product's application number, and some related exclusivities. Drug manufacturers are required to list with FDA patent information related to their drug.[2] This listing in the Orange Book is used by generic manufacturers to make development decisions as it provides information about when patents or exclusivities associated with an approved drug will expire.

While FDA has issued regulations clarifying certain types of patents that must be submitted to the agency and certain types that must not be submitted, many patents are complex and may not fall clearly into the types identified by FDA. As a result, some branded drug manufacturers may choose not to submit every patent on a product to the FDA, and others are submitting patents potentially for the purpose of blocking generic competition.[3] Further, some stakeholders have been critical that the patent information included in the Orange Book is not as accurate or up-to-date as it could be.

This legislation would help to ensure that the Orange Book is accurate and up-to-date, by specifying what information must be submitted to FDA and what information should be listed, clarifying that invalid patents must be removed in a timely manner, directing FDA to solicit public comment on the types of information that should be listed in the Orange Book an evaluation of such comments to Congress, and the GAO to study whether certain patents should, or should not be listed in the Orange Book.

COMMITTEE HEARINGS

For the purposes of section 103(i) of H. Res. 6 of the 116th Congress, the following hearing was used to develop or consider H.R. 1503:

The Subcommittee on Health held a legislative hearing on March 13, 2019, to consider H.R. 1503, the "Orange Book Transparency Act of 2019" and six other bills. The hearing was entitled, "Lowing the Cost of Prescription Drugs: Reducing Barriers to Market Competition." The Subcommittee received testimony from:

- Lou Kennedy, Chief Executive Officer and Owner, Nephron Pharmaceuticals;

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[1] Food and Drug Administration, *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)* (https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm).

[2] 21 C.F.R. 314.53

[3] Reed F Bell & Aaron S Kesselheim, *Tertiary patenting on drug—device combination products in the United States,* (https://www.nature.com/articles/nbt.4078.epdf?author_access_token=k19w_aka6yYXhVtkaCGFOdRgN0jAjWel9jnR3ZoTv0MGOAdGITA-e4st1uwIqL0ZGE0-17DL5n2Qg8u7_csdohGlFGwUWdjvieJtiDwzfoldY3_E4HS6rf7YbpkcyvI2u).

- Anthony Barrueta, Senior Vice President for Government Relations, Kaiser Permanente;
- Michael Carrier, Distinguished Professor, Rutgers Law School;
- Kurt Karst, Director, Hyman, Phelps & McNamara, P.C.;
- Jeff Kushan, Partner, Sidley Austin LLP;
- Marc M. Boutin, JD, Chief Executive Officer, National Health Council; and
- Chester "Chip" Davis, Jr., President and Chief Executive Officer, Association for Accessible Medicines.

COMMITTEE CONSIDERATION

H.R. 1503, the "Orange Book Transparency Act of 2019", was introduced on March 5, 2019, by Rep. Kelly (D–IL), and referred to the Committee on Energy and Commerce. The bill was subsequently referred to the Subcommittee on Health on March 6, 2019. Following legislative hearings, the Subcommittee met in open markup session on H.R. 1503 on March 27, 2019, pursuant to notice, for consideration of the bill. A manager's amendment offered by Ms. Kelly was adopted by a voice vote. Subsequently, the Subcommittee on Health agreed to a motion by Ms. Eshoo, Chairwoman of the Subcommittee, to favorably forward H.R. 1503 to the full Committee on Energy and Commerce, amended.

The full Committee on Energy and Commerce met in open markup session, pursuant to notice, on April 3, 2019, to consider H.R. 1503, as amended by the subcommittee. An amendment by Ms. Kelly and Mr. Guthrie was adopted by a voice vote. At the conclusion of consideration and markup of the bill, the Committee agreed to a motion by Mr. Pallone, Chairman of the Committee, to order H.R. 1503 favorably reported to the House, amended, by a voice vote.

COMMITTEE VOTES

Clause 3(b) of rule XIII of the Rules of the House of Representatives requires the Committee to list each record vote on the motion to report legislation and amendments thereto. The Committee advises that there were no record votes taken on H.R. 1503. A motion by Mr. Pallone to order H.R. 1503 favorably reported to the House, amended, was agreed to by a voice vote.

OVERSIGHT FINDINGS

Pursuant to clause 3(c)(1) of rule XIII and clause 2(b)(1) of rule X of the Rules of the House of Representatives, the oversight findings and recommendations of the Committee are reflected in the descriptive portion of the report.

NEW BUDGET AUTHORITY, ENTITLEMENT AUTHORITY, AND TAX EXPENDITURES

Pursuant to 3(c)(2) of rule XIII of the Rules of the House of Representatives, the Committee adopts as its own the estimate of new budget authority, entitlement authority, or tax expenditures or revenues contained in the cost estimate prepared by the Director of

the Congressional Budget Office pursuant to section 402 of the Congressional Budget Act of 1974.

CONGRESSIONAL BUDGET OFFICE ESTIMATE

With respect to the requirements of clause (3)(c)(3) of rule XIII of the Rules of the House of Representatives and section 402 of the Congressional Budget Act of 1974, the Committee has received the following cost estimate for H.R. 1503 from the Director of Congressional Budget Office:

U.S. CONGRESS,
CONGRESSIONAL BUDGET OFFICE,
Washington, DC, May 1, 2019.

Hon. FRANK PALLONE, Jr.,
Chairman, Committee on Energy and Commerce,
House of Representatives, Washington, DC.

DEAR MR. CHAIRMAN: The Congressional Budget Office has prepared the enclosed cost estimate for H.R. 1503, the Orange Book Transparency Act of 2019.

If you wish further details on this estimate, we will be pleased to provide them. The CBO staff contact is Julia Christensen.

Sincerely,

KEITH HALL,
Director.

Enclosure.

H.R. 1503, Orange Book Transparency Act of 2019
As ordered reported by the House Committee on Energy and Commerce on April 3, 2019

By Fiscal Year, Millions of Dollars	2019	2019-2024	2019-2029
Direct Spending (Outlays)	0	0	0
Revenues	0	0	0
Deficit Effect	0	0	0
Spending Subject to Appropriation (Outlays)	0	1	n.e.

Pay-as-you-go procedures apply?	No	Mandate Effects	
Increases on-budget deficits in any of the four consecutive 10-year periods beginning in 2030?	No	Contains intergovernmental mandate?	No
		Contains private-sector mandate?	Yes, Under Threshold

n.e. = not estimated.

Under current law, the Food and Drug Administration (FDA) publishes a compendium entitled, *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly referred to as the "Orange Book." The Orange Book identifies drug products approved on the basis of safety and effectiveness by FDA and provides associated patent and exclusivity information. FDA updates the Orange Book on a regular basis. H.R. 1503 would codify current regulations and practice regarding the types of patent and exclusivity-related information listed in the Orange Book.

H.R. 1503 also would require the prompt removal of certain patents from the Orange Book that have been invalidated by a ruling

of the Patent Trial and Appeal Board at the United States Patent and Trademark Office.

The bill would require FDA to solicit public comments regarding the types of patent information that should be listed in the Orange Book. Within one year of enactment, FDA would be required to transmit to the Congress an evaluation of such comments, including any recommendations about the types of patent information that should be included on or removed from such list.

In addition, H.R. 1503 would direct the General Accountability Office (GAO) to conduct a study that analyzes certain patents with claims relating to devices listed in the Orange Book and evaluates the extent to which listing such patents has affected the timing for the entry of generic drugs into the market. The bill would require GAO to submit the report to the Congress within one year of enactment.

Based on the costs of similar activities, CBO estimates that implementing the bill would cost $1 million, primarily for FDA's personnel-related expenses to comply with the bill's reporting requirements. Any such spending would be subject to the availability of appropriated funds.

H.R. 1503 would impose a private-sector mandate as defined in the Unfunded Mandates Reform Act (UMRA) by requiring drug manufacturers to notify the FDA when the Patent Trial and Appeals Board or another court finds a drug patent to be invalid. CBO estimates the cost of the mandate would fall well below the private-sector threshold established in UMRA ($164 million in 2019, adjusted annually for inflation).

The CBO staff contacts for this estimate are Julia Christensen (for federal costs) and Andrew Laughlin (for mandates). The estimate was reviewed by Leo Lex, Deputy Assistant Director for Budget Analysis.

FEDERAL MANDATES STATEMENT

The Committee adopts as its own the estimate of Federal mandates prepared by the Director of the Congressional Budget Office pursuant to section 423 of the Unfunded Mandates Reform Act.

STATEMENT OF GENERAL PERFORMANCE GOALS AND OBJECTIVES

Pursuant to clause 3(c)(4) of rule XIII, the general performance goal or objective of this legislation is to amend the Food, Drug, and Cosmetic Act to clarify which patents should be submitted to FDA, that exclusivity periods should be included on the list under 505(j)(7)(A) of the Act, and when invalid patents should be removed from that list. The bill also directs the Comptroller General to conduct a study about the types of patents that are currently included on this list and whether they should continue to be included on this list.

DUPLICATION OF FEDERAL PROGRAMS

Pursuant to clause 3(c)(5) of rule XIII, no provision of H.R. 1503 is known to be duplicative of another Federal program, including any program that was included in a report to Congress pursuant to section 21 of Public Law 111–139 or the most recent Catalog of Federal Domestic Assistance.

COMMITTEE COST ESTIMATE

Pursuant to clause 3(d)(1) of rule XIII, the Committee adopts as its own the cost estimate prepared by the Director of the Congressional Budget Office pursuant to section 402 of the Congressional Budget Act of 1974.

EARMARKS, LIMITED TAX BENEFITS, AND LIMITED TARIFF BENEFITS

Pursuant to clause 9(e), 9(f), and 9(g) of rule XXI, the Committee finds that H.R. 1503 contains no earmarks, limited tax benefits, or limited tariff benefits.

ADVISORY COMMITTEE STATEMENT

No advisory committees within the meaning of section 5(b) of the Federal Advisory Committee Act were created by this legislation.

APPLICABILITY TO LEGISLATIVE BRANCH

The Committee finds that the legislation does not relate to the terms and conditions of employment or access to public services or accommodations within the meaning of section 102(b)(3) of the Congressional Accountability Act.

SECTION-BY-SECTION ANALYSIS OF THE LEGISLATION

Section 1: Short title

This Act may be cited as the "Orange Book Transparency Act of 2019".

Section 2: Orange Book

Subsection (a) amends section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) to require FDA to include the following patent information for a drug in the Orange Book: drug substance patents, drug product patents, and method of use patents.

Subsection (b) amends the requirements for subsequent submissions of patent information in Section 505(c)(2) to conform to the clarified requirements in 505(b).

Subsection (c) requires the Secretary to specify each exclusivity period for drugs listed in the Orange Book.

Subsection (d) requires that approved drug application holders promptly notify FDA if one of their listed patents is found invalid in a decision from either the Patent Trial and Appeals Board or a court issues a decision from which no appeal has been or can be taken. The legislation further requires that FDA remove a patent from this list promptly if it is found to be invalid, but not before the expiration of any 180-day exclusivity period.

Subsection (e) requires FDA to solicit public comment regarding the types of patent information that should be included on the "Orange Book" and transmit to Congress an evaluation of such comments, including any recommendations about the types of information that should be included or removed from the list.

Section 3: GAO report to Congress

Section 3 directs GAO to analyze and evaluate the types of patents included in the Orange Book and the claims such patents

make about the products they claim, and to include in such analysis specific data and recommendations about the types of patents that should be listed.

CHANGES IN EXISTING LAW MADE BY THE BILL, AS REPORTED

In compliance with clause 3(e) of rule XIII of the Rules of the House of Representatives, changes in existing law made by the bill, as reported, are shown as follows (existing law proposed to be omitted is enclosed in black brackets, new matter is printed in italic, and existing law in which no change is proposed is shown in roman):

FEDERAL FOOD, DRUG, AND COSMETIC ACT

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CHAPTER V—DRUGS AND DEVICES

SUBCHAPTER A—DRUGS AND DEVICES

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NEW DRUGS

SEC. 505. (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug.

(b)[(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (B) a full list of the articles used as components of such drug; (C) a full statement of the composition of such drug; (D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (E) such samples of such drug and of the articles used as components thereof as the Secretary may require; (F) specimens of the labeling proposed to be used for such drug, and (G) any assessments required under section 505B. The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture use, or sale of the drug. If a application is filed under this subsection for a drug and a patent which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include the information required by the preceding sentence. Upon approval of the application, the Secretary shall publish information submitted under the two preceding sentences. The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appro-

priate, on the inclusion of women and minorities in clinical trials required by clause (A).] *(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as part of the application—*

(A) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use;

(B) a full list of the articles used as components of such drug;

(C) a full statement of the composition of such drug;

(D) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug;

(E) such samples of such drug and of the articles used as components thereof as the Secretary may require;

(F) specimens of the labeling proposed to be used for such drug;

(G) any assessments required under section 505B; and

(H) patent information, with respect to each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug, and consistent with the following requirements:

(i) The applicant shall file with the application the patent number and the expiration date of—

(I) any patent which claims the drug for which the applicant submitted the application and is a drug substance (including active ingredient) patent or a drug product (including formulation and composition) patent; and

(II) any patent which claims the method of using such drug.

(ii) If an application is filed under this subsection for a drug and a patent of the type described in clause (i) which claims such drug or a method of using such drug is issued after the filing date but before approval of the application, the applicant shall amend the application to include such patent information.

Upon approval of the application, the Secretary shall publish the information submitted under subparagraph (H). The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials required by subparagraph (A).

(2) An application submitted under paragraph (1) for a drug for which the investigations described in clause (A) of such paragraph and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include—

(A) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the drug for which such investigations were conducted or

which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c)—

(i) that such patent information has not been filed,

(ii) that such patent has expired,

(iii) of the date on which such patent will expire, or

(iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in paragraph (1)(A) were conducted information was filed under paragraph (1) or subsection (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

(3) NOTICE OF OPINION THAT PATENT IS INVALID OR WILL NOT BE INFRINGED.—

(A) AGREEMENT TO GIVE NOTICE.—An applicant that makes a certification described in paragraph (2)(A)(iv) shall include in the application a statement that the applicant will give notice as required by this paragraph.

(B) TIMING OF NOTICE.—An applicant that makes a certification described in paragraph (2)(A)(iv) shall give notice as required under this paragraph—

(i) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(ii) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(C) RECIPIENTS OF NOTICE.—An applicant required under this paragraph to give notice shall give notice to—

(i) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(ii) the holder of the approved application under this subsection for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(D) CONTENTS OF NOTICE.—A notice required under this paragraph shall—

(i) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(ii) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(4)(A) An applicant may not amend or supplement an application referred to in paragraph (2) to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the Secretary.

(B) With respect to the drug for which such an application is submitted, nothing in this subsection or subsection (c)(3) prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(5)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1) or under section 351 of the Public Health Service Act, which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection or section 351 of the Public Health Service Act if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size—

(i)(I) of clinical trials intended to form the primary basis of an effectiveness claim; or

(II) in the case where human efficacy studies are not ethical or feasible, of animal and any associated clinical trials which, in combination, are intended to form the primary basis of an effectiveness claim; or

(ii) with respect to an application for approval of a biological product under section 351(k) of the Public Health Service Act, of any necessary clinical study or studies.

The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of the clinical trials. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant upon request.

(C) Any agreement regarding the parameters of the design and size of clinical trials of a new drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the administrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance division personnel unless such field or compliance division personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection or section 351 of the Public Health Service Act (including all scientific and medical matters, chemistry, manufacturing, and controls).

(6) An application submitted under this subsection shall be accompanied by the certification required under section 402(j)(5)(B) of the Public Health Service Act. Such certification shall not be considered an element of such application.

(c)(1) Within one hundred and eighty days after the filing of an application under subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(A) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(2) If the patent information described in subsection (b) could not be filed with the submission of an application under subsection (b) because the application was filed before the patent information was required under subsection (b) or a patent was issued after the application was approved under such subsection, the holder of an approved application shall file with the Secretary, the patent number and the expiration date of any patent which *fulfills the criteria in subsection (b) and* claims the drug for which the application was submitted or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug. *Patent information that is not the type of patent information required by subsection (b) shall not be submitted.* If the holder of an approved application could not file patent information under subsection (b) because it was not required at the time the application was approved, the holder shall file such information under this subsection not later than thirty days after the date of the enactment of this sentence, and if the holder of an approved application could not file patent information

under subsection (b) because no patent *of the type required to be submitted in subsection (b)* had been issued when an application was filed or approved, the holder shall file such information under this subsection not later than thirty days after after the date the patent involved is issued. Upon the submission of patent information under this subsection, the Secretary shall publish it.

(3) The approval of an application filed under subsection (b) which contains a certification required by paragraph (2) of such subsection shall be made effective on the last applicable date determined by applying the following to each certification made under subsection (b)(2)(A):

(A) If the applicant only made a certification described in clause (i) or (ii) of subsection (b)(2)(A) or in both such clauses, the approval may be made effective immediately.

(B) If the applicant made a certification described in clause (iii) of subsection (b)(2)(A), the approval may be made effective on the date certified under clause (iii).

(C) If the applicant made a certification described in clause (iv) of subsection (b)(2)(A), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in subsection (b)(3) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under paragraph (2) or subsection (b)(1) before the date on which the application (excluding an amendment or supplement to the application) was submitted. If such an action is brought before the expiration of such days, the approval may be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under subsection (b)(3) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(i) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(I) the date on which the court enters judgment reflecting the decision; or

(II) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(ii) if before the expiration of such period the district court decides that the patent has been infringed—

(I) if the judgment of the district court is appealed, the approval shall be made effective on—

(aa) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity); or

(bb) the date of a settlement order or consent decree signed and entered by the court of appeals

stating that the patent that is the subject of the certification is invalid or not infringed; or

(II) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of title 35, United States Code;

(iii) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in clause (i); or

(iv) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in clause (ii).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(D) CIVIL ACTION TO OBTAIN PATENT CERTAINTY.—

(i) DECLARATORY JUDGMENT ABSENT INFRINGEMENT ACTION.—

(I) IN GENERAL.—No action may be brought under section 2201 of title 28, United States Code, by an applicant referred to in subsection (b)(2) for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (C) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) FILING OF CIVIL ACTION.—If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of title 28, United States Code, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the

patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) OFFER OF CONFIDENTIAL ACCESS TO APPLICATION.—For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant referred to in subsection (b)(2) for the purpose of determining whether an action referred to in subparagraph (C) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under subsection (b)(2)(A)(iv) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) COUNTERCLAIM TO INFRINGEMENT ACTION.—

(I) IN GENERAL.—If an owner of the patent or the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or this subsection on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) NO INDEPENDENT CAUSE OF ACTION.—Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) NO DAMAGES.—An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(E)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection, the Secretary may not make the approval of another application for a drug for which the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted effective before the expiration of ten years from the date of the approval of the application previously approved under subsection (b).

(ii) If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this clause, no application which refers to the drug for which the subsection (b) application was submitted and for which the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted may be submitted under subsection (b) before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under subsection (b) after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in clause (iv) of subsection (b)(2)(A). The approval of such an application shall be made effective in accordance with this paragraph except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (C) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of the enactment of this clause and if such appli-

cation contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under subsection (b) for the conditions of approval of such drug in the approved subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(iv) If a supplement to an application approved under subsection (b) is approved after the date of enactment of this clause and the supplement contains reports of new clinical investigations (other than bioavailabilty studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under subsection (b) for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b) if the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and if the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

(v) If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this clause, the Secretary may not make the approval of an application submitted under this subsection and for which the investigations described in clause (A) of subsection (b)(1) and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted and which refers to the drug for which the subsection (b) application was submitted effective before the expiration of two years from the date of enactment of this clause.

(4) A drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the drug and to obtain approval for the drug prior to manufacture of the drug in a larger facility, unless the Secretary makes a determination that a full scale production facility is necessary to ensure the safety or effectiveness of the drug.

(5)(A) The Secretary may rely upon qualified data summaries to support the approval of a supplemental application, with respect to a qualified indication for a drug, submitted under subsection (b), if such supplemental application complies with subparagraph (B).

(B) A supplemental application is eligible for review as described in subparagraph (A) only if—

(i) there is existing data available and acceptable to the Secretary demonstrating the safety of the drug; and

(ii) all data used to develop the qualified data summaries are submitted to the Secretary as part of the supplemental application.

(C) The Secretary shall post on the Internet website of the Food and Drug Administration and update annually—

(i) the number of applications reviewed solely under subparagraph (A) or section 351(a)(2)(E) of the Public Health Service Act;

(ii) the average time for completion of review under subparagraph (A) or section 351(a)(2)(E) of the Public Health Service Act;

(iii) the average time for review of supplemental applications where the Secretary did not use review flexibility under subparagraph (A) or section 351(a)(2)(E) of the Public Health Service Act; and

(iv) the number of applications reviewed under subparagraph (A) or section 351(a)(2)(E) of the Public Health Service Act for which the Secretary made use of full data sets in addition to the qualified data summary.

(D) In this paragraph—

(i) the term "qualified indication" means an indication for a drug that the Secretary determines to be appropriate for summary level review under this paragraph; and

(ii) the term "qualified data summary" means a summary of clinical data that demonstrates the safety and effectiveness of a drug with respect to a qualified indication.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) the application failed to contain the patent information prescribed by subsection (b); or (7) based on a fair evaluation of all material facts, such labeling is

false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof. If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence. The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for marketing approval of a drug.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new information before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) the patent information prescribed by subsection (c) was not filed within thirty days after the receipt of written notice from the Secretary specifying the failure to file such information; or (5) that the application contains any untrue statement of a material fact: *Provided,* That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The

Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (k) or to comply with the notice requirements of section 510(k)(2), or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based. The Secretary may withdraw the approval of an application submitted under this section, or suspend the approval of such an application, as provided under this subsection, without first ordering the applicant to submit an assessment of the approved risk evaluation and mitigation strategy for the drug under section 505–1(g)(2)(D).

(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the

record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i)(1) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(A) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, or preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(B) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings;

(C) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b); and

(D) the submission to the Secretary by the manufacturer or the sponsor of the investigation of a new drug of a statement of intent regarding whether the manufacturer or

sponsor has plans for assessing pediatric safety and efficacy.

(2) Subject to paragraph (3), a clinical investigation of a new drug may begin 30 days after the Secretary has received from the manufacturer or sponsor of the investigation a submission containing such information about the drug and the clinical investigation, including—

(A) information on design of the investigation and adequate reports of basic information, certified by the applicant to be accurate reports, necessary to assess the safety of the drug for use in clinical investigation; and

(B) adequate information on the chemistry and manufacturing of the drug, controls available for the drug, and primary data tabulations from animal or human studies.

(3)(A) At any time, the Secretary may prohibit the sponsor of an investigation from conducting the investigation (referred to in this paragraph as a "clinical hold") if the Secretary makes a determination described in subparagraph (B). The Secretary shall specify the basis for the clinical hold, including the specific information available to the Secretary which served as the basis for such clinical hold, and confirm such determination in writing.

(B) For purposes of subparagraph (A), a determination described in this subparagraph with respect to a clinical hold is that—

(i) the drug involved represents an unreasonable risk to the safety of the persons who are the subjects of the clinical investigation, taking into account the qualifications of the clinical investigators, information about the drug, the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved; or

(ii) the clinical hold should be issued for such other reasons as the Secretary may by regulation establish (including reasons established by regulation before the date of the enactment of the Food and Drug Administration Modernization Act of 1997).

(C) Any written request to the Secretary from the sponsor of an investigation that a clinical hold be removed shall receive a decision, in writing and specifying the reasons therefor, within 30 days after receipt of such request. Any such request shall include sufficient information to support the removal of such clinical hold.

(4) Regulations under paragraph (1) shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where it is not feasible, it is contrary to the best interests of such human beings, or the proposed clinical testing poses no more than minimal risk to such human beings and includes appropriate safeguards as prescribed to protect the rights, safety, and welfare of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs. The Secretary shall update such regula-

tions to require inclusion in the informed consent documents and process a statement that clinical trial information for such clinical investigation has been or will be submitted for inclusion in the registry data bank pursuant to subsection (j) of section 402 of the Public Health Service Act.

(j)(1) Any person may file with the Secretary an abbreviated application for the approval of a new drug.

(2)(A) An abbreviated application for a new drug shall contain—

(i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed under paragraph (7) (hereinafter in this subsection referred to as a "listed drug");

(ii)(I) if the listed drug referred to in clause (i) has only one active ingredient, information to show that the active ingredient of the new drug is the same as that of the listed drug;

(II) if the listed drug referred to in clause (i) has more than one active ingredient, information to show that the active ingredients of the new drug are the same as those of the listed drug, or

(III) if the listed drug referred to in clause (i) has more than one active ingredient and if one of the active ingredients of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the other active ingredients of the new drug are the same as the active ingredients of the listed drug, information to show that the different active ingredient is an active ingredient of a listed drug or of a drug which does not meet the requirements of section 201(p), and such other information respecting the different active ingredient with respect to which the petition was filed as the Secretary may require;

(iii) information to show that the route of administration, the dosage form, and the strength of the new drug are the same as those of the listed drug referred to in clause (i) or, if the route of administration, the dosage form, or the strength of the new drug is different and the application is filed pursuant to the approval of a petition filed under subparagraph (C), such information respecting the route of administration, dosage form, or strength with respect to which the petition was filed as the Secretary may require;

(iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i), except that if the application is filed pursuant to the approval of a petition filed under subparagraph (C), information to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in clause (i) and the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in clause (i);

(v) information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers;

(vi) the items specified in clauses (B) through (F) of subsection (b)(1);

(vii) a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug referred to in clause (i) or which claims a use for such listed drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under subsection (b) or (c)—

(I) that such patent information has not been filed,

(II) that such patent has expired,

(III) of the date on which such patent will expire, or

(IV) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(viii) if with respect to the listed drug referred to in clause (i) information was filed under subsection (b) or (c) for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

The Secretary may not require that an abbreviated application contain information in addition to that required by clauses (i) through (viii).

(B) NOTICE OF OPINION THAT PATENT IS INVALID OR WILL NOT BE INFRINGED.—

(i) AGREEMENT TO GIVE NOTICE.—An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall include in the application a statement that the applicant will give notice as required by this subparagraph.

(ii) TIMING OF NOTICE.—An applicant that makes a certification described in subparagraph (A)(vii)(IV) shall give notice as required under this subparagraph—

(I) if the certification is in the application, not later than 20 days after the date of the postmark on the notice with which the Secretary informs the applicant that the application has been filed; or

(II) if the certification is in an amendment or supplement to the application, at the time at which the applicant submits the amendment or supplement, regardless of whether the applicant has already given notice with respect to another such certification contained in the application or in an amendment or supplement to the application.

(iii) RECIPIENTS OF NOTICE.—An applicant required under this subparagraph to give notice shall give notice to—

(I) each owner of the patent that is the subject of the certification (or a representative of the owner designated to receive such a notice); and

(II) the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent (or a representative of the holder designated to receive such a notice).

(iv) CONTENTS OF NOTICE.—A notice required under this subparagraph shall—

(I) state that an application that contains data from bioavailability or bioequivalence studies has been submitted under this subsection for the drug with respect to which

the certification is made to obtain approval to engage in the commercial manufacture, use, or sale of the drug before the expiration of the patent referred to in the certification; and

(II) include a detailed statement of the factual and legal basis of the opinion of the applicant that the patent is invalid or will not be infringed.

(C) If a person wants to submit an abbreviated application for a new drug which has a different active ingredient or whose route of administration, dosage form, or strength differ from that of a listed drug, such person shall submit a petition to the Secretary seeking permission to file such an application. The Secretary shall approve or disapprove a petition submitted under this subparagraph within ninety days of the date the petition is submitted. The Secretary shall approve such a petition unless the Secretary finds—

(i) that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug; or

(ii) that any drug with a different active ingredient may not be adequately evaluated for approval as safe and effective on the basis of the information required to be submitted in an abbreviated application.

(D)(i) An applicant may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary.

(ii) With respect to the drug for which an application is submitted, nothing in this subsection prohibits an applicant from amending or supplementing the application to seek approval of a different strength.

(iii) Within 60 days after the date of the enactment of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, the Secretary shall issue guidance defining the term "listed drug" for purposes of this subparagraph.

(3)(A) The Secretary shall issue guidance for the individuals who review applications submitted under paragraph (1), which shall relate to promptness in conducting the review, technical excellence, lack of bias and conflict of interest, and knowledge of regulatory and scientific standards, and which shall apply equally to all individuals who review such applications.

(B) The Secretary shall meet with a sponsor of an investigation or an applicant for approval for a drug under this subsection if the sponsor or applicant makes a reasonable written request for a meeting for the purpose of reaching agreement on the design and size of bioavailability and bioequivalence studies needed for approval of such application. The sponsor or applicant shall provide information necessary for discussion and agreement on the design and size of such studies. Minutes of any such meeting shall be prepared by the Secretary and made available to the sponsor or applicant.

(C) Any agreement regarding the parameters of design and size of bioavailability and bioequivalence studies of a drug under this paragraph that is reached between the Secretary and a sponsor or applicant shall be reduced to writing and made part of the admin-

istrative record by the Secretary. Such agreement shall not be changed after the testing begins, except—

(i) with the written agreement of the sponsor or applicant; or

(ii) pursuant to a decision, made in accordance with subparagraph (D) by the director of the reviewing division, that a substantial scientific issue essential to determining the safety or effectiveness of the drug has been identified after the testing has begun.

(D) A decision under subparagraph (C)(ii) by the director shall be in writing and the Secretary shall provide to the sponsor or applicant an opportunity for a meeting at which the director and the sponsor or applicant will be present and at which the director will document the scientific issue involved.

(E) The written decisions of the reviewing division shall be binding upon, and may not directly or indirectly be changed by, the field or compliance office personnel unless such field or compliance office personnel demonstrate to the reviewing division why such decision should be modified.

(F) No action by the reviewing division may be delayed because of the unavailability of information from or action by field personnel unless the reviewing division determines that a delay is necessary to assure the marketing of a safe and effective drug.

(G) For purposes of this paragraph, the reviewing division is the division responsible for the review of an application for approval of a drug under this subsection (including scientific matters, chemistry, manufacturing, and controls).

(4) Subject to paragraph (5), the Secretary shall approve an application for a drug unless the Secretary finds—

(A) the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;

(B) information submitted with the application is insufficient show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application;

(C)(i) if the listed drug has only one active ingredient, information submitted with the application is insufficient to show that the active ingredient is the same as that of the listed drug;

(ii) if the listed drug has more than one active ingredient, information submitted with the application is insufficient to show that the active ingredients are the same as the active ingredients of the listed drug, or

(iii) if the listed drug has more than one active ingredient and if the application is for a drug which has an active ingredient different from the listed drug, information submitted with the application is insufficient to show—

(I) that the other active ingredients are the same as the active ingredients of the listed drug, or

(II) that the different active ingredient is an active ingredient of a listed drug or a drug which does not meet the requirements of section 201(p),

or no petition to file an application for the drug with the different ingredient was approved under paragraph (2)(C);

(D)(i) if the application is for a drug whose route of administration, dosage form, or strength of the drug is the same as the route of administration, dosage form, or strength of the listed drug referred to in the application, information submitted in the application is insufficient to show that the route of administration, dosage form, or strength is the same as that of the listed drug, or

(ii) if the application is for a drug whose route of administration, dosage form, or strength of the drug is different from that of the listed drug referred to in the application, no petition to file an application for the drug with the different route of administration, dosage form, or strength was approved under paragraph (2)(C);

(E) if the application was filed pursuant to the approval of a petition under paragraph (2)(C), the application did not contain the information required by the Secretary respecting the active ingredient, route of administration, dosage form, or strength which is not the same;

(F) information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application or, if the application was filed pursuant to a petition approved under paragraph (2)(C), information submitted in the application is insufficient to show that the active ingredients of the new drug are of the same pharmacological or therapeutic class as those of the listed drug referred to in paragraph (2)(A)(i) and that the new drug can be expected to have the same therapeutic effect as the listed drug when administered to patients for a condition of use referred to in such paragraph;

(G) information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the application except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;

(H) information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drug is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included;

(I) the approval under subsection (c) of the listed drug referred to in the application under this subsection has been withdrawn or suspended for grounds described in the first sentence of subsection (e), the Secretary has published a notice of opportunity for hearing to withdraw approval of the listed drug under subsection (c) for grounds described in the first sentence of subsection (e), the approval under this subsection of the listed drug referred to in the application under this subsection has been withdrawn or suspended under paragraph (6), or the Sec-

retary has determined that the listed drug has been withdrawn from sale for safety or effectiveness reasons;

(J) the application does not meet any other requirement of paragraph (2)(A); or

(K) the application contains an untrue statement of material fact.

(5)(A) Within one hundred and eighty days of the initial receipt of an application under paragraph (2) or within such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall approve or disapprove the application.

(B) The approval of an application submitted under paragraph (2) shall be made effective on the last applicable date determined by applying the following to each certification made under paragraph (2)(A)(vii):

(i) If the applicant only made a certification described in subclause (I) or (II) of paragraph (2)(A)(vii) or in both such subclauses, the approval may be made effective immediately.

(ii) If the applicant made a certification described in subclause (III) of paragraph (2)(A)(vii), the approval may be made effective on the date certified under subclause (III).

(iii) If the applicant made a certification described in subclause (IV) of paragraph (2)(A)(vii), the approval shall be made effective immediately unless, before the expiration of 45 days after the date on which the notice described in paragraph (2)(B) is received, an action is brought for infringement of the patent that is the subject of the certification and for which information was submitted to the Secretary under subsection (b)(1) or (c)(2) before the date on which the application (excluding an amendment or supplement to the application), which the Secretary later determines to be substantially complete, was submitted. If such an action is brought before the expiration of such days, the approval shall be made effective upon the expiration of the thirty-month period beginning on the date of the receipt of the notice provided under paragraph (2)(B)(i) or such shorter or longer period as the court may order because either party to the action failed to reasonably cooperate in expediting the action, except that—

(I) if before the expiration of such period the district court decides that the patent is invalid or not infringed (including any substantive determination that there is no cause of action for patent infringement or invalidity), the approval shall be made effective on—

(aa) the date on which the court enters judgment reflecting the decision; or

(bb) the date of a settlement order or consent decree signed and entered by the court stating that the patent that is the subject of the certification is invalid or not infringed;

(II) if before the expiration of such period the district court decides that the patent has been infringed—

(aa) if the judgment of the district court is appealed, the approval shall be made effective on—

(AA) the date on which the court of appeals decides that the patent is invalid or not infringed (including any substantive determination that

there is no cause of action for patent infringement or invalidity); or

(BB) the date of a settlement order or consent decree signed and entered by the court of appeals stating that the patent that is the subject of the certification is invalid or not infringed; or

(bb) if the judgment of the district court is not appealed or is affirmed, the approval shall be made effective on the date specified by the district court in a court order under section 271(e)(4)(A) of title 35, United States Code;

(III) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent is invalid or not infringed, the approval shall be made effective as provided in subclause (I); or

(IV) if before the expiration of such period the court grants a preliminary injunction prohibiting the applicant from engaging in the commercial manufacture or sale of the drug until the court decides the issues of patent validity and infringement and if the court decides that such patent has been infringed, the approval shall be made effective as provided in subclause (II).

In such an action, each of the parties shall reasonably cooperate in expediting the action.

(iv) 180-DAY EXCLUSIVITY PERIOD.—

(I) EFFECTIVENESS OF APPLICATION.—Subject to subparagraph (D), if the application contains a certification described in paragraph (2)(A)(vii)(IV) and is for a drug for which a first applicant has submitted an application containing such a certification, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant.

(II) DEFINITIONS.—In this paragraph:

(aa) 180-DAY EXCLUSIVITY PERIOD.—The term "180-day exclusivity period" means the 180-day period ending on the day before the date on which an application submitted by an applicant other than a first applicant could become effective under this clause.

(bb) FIRST APPLICANT.—As used in this subsection, the term "first applicant" means an applicant that, on the first day on which a substantially complete application containing a certification described in paragraph (2)(A)(vii)(IV) is submitted for approval of a drug, submits a substantially complete application that contains and lawfully maintains a certification described in paragraph (2)(A)(vii)(IV) for the drug.

(cc) SUBSTANTIALLY COMPLETE APPLICATION.—As used in this subsection, the term "substantially complete application" means an application under this subsection that on its face is sufficiently complete to

permit a substantive review and contains all the information required by paragraph (2)(A).

(dd) TENTATIVE APPROVAL.—

(AA) IN GENERAL.—The term "tentative approval" means notification to an applicant by the Secretary that an application under this subsection meets the requirements of paragraph (2)(A), but cannot receive effective approval because the application does not meet the requirements of this subparagraph, there is a period of exclusivity for the listed drug under subparagraph (F) or section 505A, or there is a 7-year period of exclusivity for the listed drug under section 527.

(BB) LIMITATION.—A drug that is granted tentative approval by the Secretary is not an approved drug and shall not have an effective approval until the Secretary issues an approval after any necessary additional review of the application.

(v) 180-DAY EXCLUSIVITY PERIOD FOR COMPETITIVE GENERIC THERAPIES.—

(I) EFFECTIVENESS OF APPLICATION.—Subject to subparagraph (D)(iv), if the application is for a drug that is the same as a competitive generic therapy for which any first approved applicant has commenced commercial marketing, the application shall be made effective on the date that is 180 days after the date of the first commercial marketing of the competitive generic therapy (including the commercial marketing of the listed drug) by any first approved applicant.

(II) LIMITATION.—The exclusivity period under subclause (I) shall not apply with respect to a competitive generic therapy that has previously received an exclusivity period under subclause (I).

(III) DEFINITIONS.—In this clause and subparagraph (D)(iv):

(aa) The term "competitive generic therapy" means a drug—

(AA) that is designated as a competitive generic therapy under section 506H; and

(BB) for which there are no unexpired patents or exclusivities on the list of products described in section 505(j)(7)(A) at the time of submission.

(bb) The term "first approved applicant" means any applicant that has submitted an application that—

(AA) is for a competitive generic therapy that is approved on the first day on which any application for such competitive generic therapy is approved;

(BB) is not eligible for a 180-day exclusivity period under clause (iv) for the drug that is the subject of the application for the competitive generic therapy; and

(CC) is not for a drug for which all drug versions have forfeited eligibility for a 180-day ex-

clusivity period under clause (iv) pursuant to subparagraph (D).

(C) CIVIL ACTION TO OBTAIN PATENT CERTAINTY.—

(i) DECLARATORY JUDGMENT ABSENT INFRINGEMENT ACTION.—

(I) IN GENERAL.—No action may be brought under section 2201 of title 28, United States Code, by an applicant under paragraph (2) for a declaratory judgment with respect to a patent which is the subject of the certification referred to in subparagraph (B)(iii) unless—

(aa) the 45-day period referred to in such subparagraph has expired;

(bb) neither the owner of such patent nor the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brought a civil action against the applicant for infringement of the patent before the expiration of such period; and

(cc) in any case in which the notice provided under paragraph (2)(B) relates to noninfringement, the notice was accompanied by a document described in subclause (III).

(II) FILING OF CIVIL ACTION.—If the conditions described in items (aa), (bb), and as applicable, (cc) of subclause (I) have been met, the applicant referred to in such subclause may, in accordance with section 2201 of title 28, United States Code, bring a civil action under such section against the owner or holder referred to in such subclause (but not against any owner or holder that has brought such a civil action against the applicant, unless that civil action was dismissed without prejudice) for a declaratory judgment that the patent is invalid or will not be infringed by the drug for which the applicant seeks approval, except that such civil action may be brought for a declaratory judgment that the patent will not be infringed only in a case in which the condition described in subclause (I)(cc) is applicable. A civil action referred to in this subclause shall be brought in the judicial district where the defendant has its principal place of business or a regular and established place of business.

(III) OFFER OF CONFIDENTIAL ACCESS TO APPLICATION.—For purposes of subclause (I)(cc), the document described in this subclause is a document providing an offer of confidential access to the application that is in the custody of the applicant under paragraph (2) for the purpose of determining whether an action referred to in subparagraph (B)(iii) should be brought. The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and

other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

(ii) COUNTERCLAIM TO INFRINGEMENT ACTION.—

(I) IN GENERAL.—If an owner of the patent or the holder of the approved application under subsection (b) for the drug that is claimed by the patent or a use of which is claimed by the patent brings a patent infringement action against the applicant, the applicant may assert a counterclaim seeking an order requiring the holder to correct or delete the patent information submitted by the holder under subsection (b) or (c) on the ground that the patent does not claim either—

(aa) the drug for which the application was approved; or

(bb) an approved method of using the drug.

(II) NO INDEPENDENT CAUSE OF ACTION.—Subclause (I) does not authorize the assertion of a claim described in subclause (I) in any civil action or proceeding other than a counterclaim described in subclause (I).

(iii) NO DAMAGES.—An applicant shall not be entitled to damages in a civil action under clause (i) or a counterclaim under clause (ii).

(D) FORFEITURE OF 180-DAY EXCLUSIVITY PERIOD.—

(i) DEFINITION OF FORFEITURE EVENT.—In this subparagraph, the term "forfeiture event", with respect to an application under this subsection, means the occurrence of any of the following:

(I) FAILURE TO MARKET.—The first applicant fails to market the drug by the later of—

(aa) the earlier of the date that is—

(AA) 75 days after the date on which the approval of the application of the first applicant is made effective under subparagraph (B)(iii); or

(BB) 30 months after the date of submission of the application of the first applicant; or

(bb) with respect to the first applicant or any other applicant (which other applicant has received tentative approval), the date that is 75 days after the date as of which, as to each of the patents with respect to which the first applicant submitted and lawfully maintained a certification qualifying the first applicant for the 180-day exclusivity period under subparagraph (B)(iv), at least 1 of the following has occurred:

(AA) In an infringement action brought against that applicant with respect to the patent or in a declaratory judgment action brought by that applicant with respect to the patent, a court enters a final decision from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the patent is invalid or not infringed.

(BB) In an infringement action or a declaratory judgment action described in subitem (AA), a court signs a settlement order or consent decree that enters a final judgment that includes a finding that the patent is invalid or not infringed.

(CC) The patent information submitted under subsection (b) or (c) is withdrawn by the holder of the application approved under subsection (b).

(II) WITHDRAWAL OF APPLICATION.—The first applicant withdraws the application or the Secretary considers the application to have been withdrawn as a result of a determination by the Secretary that the application does not meet the requirements for approval under paragraph (4).

(III) AMENDMENT OF CERTIFICATION.—The first applicant amends or withdraws the certification for all of the patents with respect to which that applicant submitted a certification qualifying the applicant for the 180-day exclusivity period.

(IV) FAILURE TO OBTAIN TENTATIVE APPROVAL.—The first applicant fails to obtain tentative approval of the application within 30 months after the date on which the application is filed, unless the failure is caused by a change in or a review of the requirements for approval of the application imposed after the date on which the application is filed.

(V) AGREEMENT WITH ANOTHER APPLICANT, THE LISTED DRUG APPLICATION HOLDER, OR A PATENT OWNER.—The first applicant enters into an agreement with another applicant under this subsection for the drug, the holder of the application for the listed drug, or an owner of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV), the Federal Trade Commission or the Attorney General files a complaint, and there is a final decision of the Federal

Trade Commission or the court with regard to the complaint from which no appeal (other than a petition to the Supreme Court for a writ of certiorari) has been or can be taken that the agreement has violated the antitrust laws (as defined in section 1 of the Clayton Act (15 U.S.C. 12), except that the term includes section 5 of the Federal Trade Commission Act (15 U.S.C. 45) to the extent that that section applies to unfair methods of competition).

(VI) EXPIRATION OF ALL PATENTS.—All of the patents as to which the applicant submitted a certification qualifying it for the 180-day exclusivity period have expired.

(ii) FORFEITURE.—The 180-day exclusivity period described in subparagraph (B)(iv) shall be forfeited by a first applicant if a forfeiture event occurs with respect to that first applicant.

(iii) SUBSEQUENT APPLICANT.—If all first applicants forfeit the 180-day exclusivity period under clause (ii)—

(I) approval of any application containing a certification described in paragraph (2)(A)(vii)(IV) shall be made effective in accordance with subparagraph (B)(iii); and

(II) no applicant shall be eligible for a 180-day exclusivity period.

(iv) SPECIAL FORFEITURE RULE FOR COMPETITIVE GENERIC THERAPY.—The 180-day exclusivity period described in subparagraph (B)(v) shall be forfeited by a first approved applicant if the applicant fails to market the competitive generic therapy within 75 days after the date on which the approval of the first approved applicant's application for the competitive generic therapy is made effective.

(E) If the Secretary decides to disapprove an application, the Secretary shall give the applicant notice of an opportunity for a hearing before the Secretary on the question of whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(F)(i) If an application (other than an abbreviated new drug application) submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted effective before the expiration of ten years from the date of the approval of the application under subsection (b).

(ii) If an application submitted under subsection (b) for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b), is approved after the date of the enactment of this subsection, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b), except that such an application may be submitted under this subsection after the expiration of four years from the date of the approval of the subsection (b) application if it contains a certification of patent invalidity or noninfringement described in subclause (IV) of paragraph (2)(A)(vii). The approval of such an application shall be made effective in accordance with subparagraph (B) except that, if an action for patent infringement is commenced during the one-year period beginning forty-eight months after the date of the approval of the subsection (b) application, the thirty-month period referred to in subparagraph (B)(iii) shall be extended by such amount of time (if any) which is required for seven and one-half years to have elapsed from the date of approval of the subsection (b) application.

(iii) If an application submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application approved under subsection (b), is approved after the date of enactment of this subsection and if such application contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant, the Secretary may not make the approval of an application submitted under this subsection for the conditions of approval of such drug in the subsection (b) application effective before the expiration of three years from the date of the approval of the application under subsection (b) for such drug.

(iv) If a supplement to an application approved under subsection (b) is approved after the date of enactment of this subsection and the supplement contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).

(v) If an application (or supplement to an application) submitted under subsection (b) for a drug, which includes an active ingredient (including any ester or salt of the active ingredient) that has been approved in another application under subsection (b), was approved during the period beginning January 1, 1982, and ending on the date of the enactment of this subsection, the Secretary may not make the approval of an application submitted under this subsection which refers to the drug for which the subsection (b) application was submitted or which refers to a change approved in a supplement to the subsection (b) application effective before the expiration of two years from the date of enactment of this subsection.

(6) If a drug approved under this subsection refers in its approved application to a drug the approval of which was withdrawn

or suspended for grounds described in the first sentence of subsection (e) or was withdrawn or suspended under this paragraph or which, as determined by the Secretary, has been withdrawn from sale for safety or effectiveness reasons, the approval of the drug under this subsection shall be withdrawn or suspended—

(A) for the same period as the withdrawal or suspension under subsection (e) or this paragraph, or

(B) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

(7)(A)(i) Within sixty days of the date of the enactment of this subsection, the Secretary shall publish and make available to the public—

(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) before the date of the enactment of this subsection;

(II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and

(III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published.

(ii) Every thirty days after the publication of the first list under clause (i) the Secretary shall revise the list to include each drug which has been approved for safety and effectiveness under subsection (c) or approved under this subsection during the thirty-day period.

(iii) When patent information submitted under subsection (b) or (c) respecting a drug included on the list is to be published by the Secretary, the Secretary shall, in revisions made under clause (ii), include such information for such drug.

(iv) For each drug included on the list, the Secretary shall specify each exclusivity period that is applicable and has not concluded under—

(I) clause (ii), (iii), or (iv) of subsection (c)(3)(E) of this section;

(II) clause (iv) or (v) of paragraph (5)(B) of this subsection;

(III) clause (ii), (iii), or (iv) of paragraph (5)(F) of this subsection;

(IV) section 505A;

(V) section 505E; or

(VI) section 527(a).

(B) A drug approved for safety and effectiveness under subsection (c) or approved under this subsection shall, for purposes of this subsection, be considered to have been published under subparagraph (A) on the date of its approval or the date of enactment, whichever is later.

(C) If the approval of a drug was withdrawn or suspended for grounds described in the first sentence of subsection (e) or was withdrawn or suspended under paragraph (6) or if the Secretary determines that a drug has been withdrawn from sale for safety or effectiveness reasons, it may not be published in the list under subparagraph (A) or, if the withdrawal or suspension occurred after its

publication in such list, it shall be immediately removed from such list—

(i) for the same period as the withdrawal or suspension under subsection (e) or paragraph (6), or

(ii) if the listed drug has been withdrawn from sale, for the period of withdrawal from sale or, if earlier, the period ending on the date the Secretary determines that the withdrawal from sale is not for safety or effectiveness reasons.

A notice of the removal shall be published in the Federal Register.

(D)(i) The holder of an application approved under subsection (c) for a drug on the list shall notify within 14 days the Secretary in writing if either of the following occurs:

(I) The Patent Trial and Appeals Board issues a decision from which no appeal has been or can be taken that a patent for such drug is invalid.

(II) A court issues a decision from which no appeal has been or can be taken that a patent for such drug is invalid.

(ii) The holder of an approved application shall include in any notification under clause (i) a copy of the decision described in subclause (I) or (II) of clause (i).

(iii) The Secretary shall remove from the list any patent that is determined to be invalid in a decision described in subclause (I) or (II) of clause (i)—

(I) promptly; but

(II) not before the expiration of any 180-day exclusivity period under paragraph (5)(B)(iv) that relies on a certification described in paragraph (2)(A)(vii)(IV) that such patent was invalid.

(8) For purposes of this subsection:

(A)(i) The term "bioavailability" means the rate and extent to which the active ingredient or therapeutic ingredient is absorbed from a drug and becomes available at the site of drug action.

(ii) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action.

(B) A drug shall be considered to be bioequivalent to a listed drug if—

(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or

(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug

concentrations on chronic use, and is considered medically insignificant for the drug.

(C) For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.

(9) The Secretary shall, with respect to each application submitted under this subsection, maintain a record of—

(A) the name of the applicant,

(B) the name of the drug covered by the application,

(C) the name of each person to whom the review of the chemistry of the application was assigned and the date of such assignment, and

(D) the name of each person to whom the bioequivalence review for such application was assigned and the date of such assignment.

The information the Secretary is required to maintain under this paragraph with respect to an application submitted under this subsection shall be made available to the public after the approval of such application.

(10)(A) If the proposed labeling of a drug that is the subject of an application under this subsection differs from the listed drug due to a labeling revision described under clause (i), the drug that is the subject of such application shall, notwithstanding any other provision of this Act, be eligible for approval and shall not be considered misbranded under section 502 if—

(i) the application is otherwise eligible for approval under this subsection but for expiration of patent, an exclusivity period, or of a delay in approval described in paragraph (5)(B)(iii), and a revision to the labeling of the listed drug has been approved by the Secretary within 60 days of such expiration;

(ii) the labeling revision described under clause (i) does not include a change to the "Warnings" section of the labeling;

(iii) the sponsor of the application under this subsection agrees to submit revised labeling of the drug that is the subject of such application not later than 60 days after the notification of any changes to such labeling required by the Secretary; and

(iv) such application otherwise meets the applicable requirements for approval under this subsection.

(B) If, after a labeling revision described in subparagraph (A)(i), the Secretary determines that the continued presence in interstate commerce of the labeling of the listed drug (as in effect before the revision described in subparagraph (A)(i)) adversely impacts the safe use of the drug, no application under this subsection shall be eligible for approval with such labeling.

(11)(A) Subject to subparagraph (B), the Secretary shall prioritize the review of, and act within 8 months of the date of the submission of, an original abbreviated new drug application submitted for review under this subsection that is for a drug—

(i) for which there are not more than 3 approved drug products listed under paragraph (7) and for which there are no blocking patents and exclusivities; or

(ii) that has been included on the list under section 506E.

(B) To qualify for priority review under this paragraph, not later than 60 days prior to the submission of an application described in subparagraph (A) or that the Secretary may prioritize pursuant to subparagraph (D), the applicant shall provide complete, accurate information regarding facilities involved in manufacturing processes and testing of the drug that is the subject of the application, including facilities in corresponding Type II active pharmaceutical ingredients drug master files referenced in an application and sites or organizations involved in bioequivalence and clinical studies used to support the application, to enable the Secretary to make a determination regarding whether an inspection of a facility is necessary. Such information shall include the relevant (as determined by the Secretary) sections of such application, which shall be unchanged relative to the date of the submission of such application, except to the extent that a change is made to such information to exclude a facility that was not used to generate data to meet any application requirements for such submission and that is not the only facility intended to conduct one or more unit operations in commercial production. Information provided by an applicant under this subparagraph shall not be considered the submission of an application under this subsection.

(C) The Secretary may expedite an inspection or reinspection under section 704 of an establishment that proposes to manufacture a drug described in subparagraph (A).

(D) Nothing in this paragraph shall prevent the Secretary from prioritizing the review of other applications as the Secretary determines appropriate.

(12) The Secretary shall publish on the internet website of the Food and Drug Administration, and update at least once every 6 months, a list of all drugs approved under subsection (c) for which all patents and periods of exclusivity under this Act have expired and for which no application has been approved under this subsection.

(13) Upon the request of an applicant regarding one or more specified pending applications under this subsection, the Secretary shall, as appropriate, provide review status updates indicating the categorical status of the applications by each relevant review discipline.

(k)(1) In the case of any drug for which an approval of an application filed under subsection (b) or (j) is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section. Regulations and orders issued under this subsection and under subsection (i) shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

(3) ACTIVE POSTMARKET RISK IDENTIFICATION.—

(A) DEFINITION.—In this paragraph, the term "data" refers to information with respect to a drug approved under this section or under section 351 of the Public Health Service Act, including claims data, patient survey data, standardized analytic files that allow for the pooling and analysis of data from disparate data environments, and any other data deemed appropriate by the Secretary.

(B) DEVELOPMENT OF POSTMARKET RISK IDENTIFICATION AND ANALYSIS METHODS.—The Secretary shall, not later than 2 years after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, in collaboration with public, academic, and private entities—

(i) develop methods to obtain access to disparate data sources including the data sources specified in subparagraph (C);

(ii) develop validated methods for the establishment of a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with the goals of including, in aggregate—

(I) at least 25,000,000 patients by July 1, 2010; and

(II) at least 100,000,000 patients by July 1, 2012; and

(iii) convene a committee of experts, including individuals who are recognized in the field of protecting data privacy and security, to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data specified under subparagraph (C), including recommendations on the development of effective research methods for the study of drug safety questions.

(C) ESTABLISHMENT OF THE POSTMARKET RISK IDENTIFICATION AND ANALYSIS SYSTEM.—

(i) IN GENERAL.—The Secretary shall, not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), establish and maintain procedures—

(I) for risk identification and analysis based on electronic health data, in compliance with the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996, and in a manner that does not disclose individually identifiable health information in violation of paragraph (4)(B);

(II) for the reporting (in a standardized form) of data on all serious adverse drug experiences (as defined in section 505–1(b)) submitted to the Secretary under paragraph (1), and those adverse

events submitted by patients, providers, and drug sponsors, when appropriate;

(III) to provide for active adverse event surveillance using the following data sources, as available:

(aa) Federal health-related electronic data (such as data from the Medicare program and the health systems of the Department of Veterans Affairs);

(bb) private sector health-related electronic data (such as pharmaceutical purchase data and health insurance claims data); and

(cc) other data as the Secretary deems necessary to create a robust system to identify adverse events and potential drug safety signals;

(IV) to identify certain trends and patterns with respect to data accessed by the system;

(V) to provide regular reports to the Secretary concerning adverse event trends, adverse event patterns, incidence and prevalence of adverse events, and other information the Secretary determines appropriate, which may include data on comparative national adverse event trends; and

(VI) to enable the program to export data in a form appropriate for further aggregation, statistical analysis, and reporting.

(ii) TIMELINESS OF REPORTING.—The procedures established under clause (i) shall ensure that such data are accessed, analyzed, and reported in a timely, routine, and systematic manner, taking into consideration the need for data completeness, coding, cleansing, and standardized analysis and transmission.

(iii) PRIVATE SECTOR RESOURCES.—To ensure the establishment of the active postmarket risk identification and analysis system under this subsection not later than 1 year after the development of the risk identification and analysis methods under subparagraph (B), as required under clause (i), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(iv) COMPLEMENTARY APPROACHES.—To the extent the active postmarket risk identification and analysis system under this subsection is not sufficient to gather data and information relevant to a priority drug safety question, the Secretary shall develop, support, and participate in complementary approaches to gather and analyze such data and information, including—

(I) approaches that are complementary with respect to assessing the safety of use of a drug in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children); and

(II) existing approaches such as the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink or successor databases.

(v) AUTHORITY FOR CONTRACTS.—The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subparagraph.

(4) ADVANCED ANALYSIS OF DRUG SAFETY DATA.—

(A) PURPOSE.—The Secretary shall establish collaborations with public, academic, and private entities, which may include the Centers for Education and Research on Therapeutics under section 912 of the Public Health Service Act, to provide for advanced analysis of drug safety data described in paragraph (3)(C) and other information that is publicly available or is provided by the Secretary, in order to—

(i) improve the quality and efficiency of postmarket drug safety risk-benefit analysis;

(ii) provide the Secretary with routine access to outside expertise to study advanced drug safety questions; and

(iii) enhance the ability of the Secretary to make timely assessments based on drug safety data.

(B) PRIVACY.—Such analysis shall not disclose individually identifiable health information when presenting such drug safety signals and trends or when responding to inquiries regarding such drug safety signals and trends.

(C) PUBLIC PROCESS FOR PRIORITY QUESTIONS.—At least biannually, the Secretary shall seek recommendations from the Drug Safety and Risk Management Advisory Committee (or any successor committee) and from other advisory committees, as appropriate, to the Food and Drug Administration on—

(i) priority drug safety questions; and

(ii) mechanisms for answering such questions, including through—

(I) active risk identification under paragraph (3); and

(II) when such risk identification is not sufficient, postapproval studies and clinical trials under subsection (o)(3).

(D) PROCEDURES FOR THE DEVELOPMENT OF DRUG SAFETY COLLABORATIONS.—

(i) IN GENERAL.—Not later than 180 days after the date of the establishment of the active postmarket risk identification and analysis system under this subsection, the Secretary shall establish and implement procedures under which the Secretary may routinely contract with one or more qualified entities to—

(I) classify, analyze, or aggregate data described in paragraph (3)(C) and information that is publicly available or is provided by the Secretary;

(II) allow for prompt investigation of priority drug safety questions, including—

(aa) unresolved safety questions for drugs or classes of drugs; and

(bb) for a newly-approved drugs, safety signals from clinical trials used to approve the drug and other preapproval trials; rare, serious drug side effects; and the safety of use in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as older people, people with comorbidities, pregnant women, or children);

(III) perform advanced research and analysis on identified drug safety risks;

(IV) focus postapproval studies and clinical trials under subsection (o)(3) more effectively on cases for which reports under paragraph (1) and other safety signal detection is not sufficient to resolve whether there is an elevated risk of a serious adverse event associated with the use of a drug; and

(V) carry out other activities as the Secretary deems necessary to carry out the purposes of this paragraph.

(ii) REQUEST FOR SPECIFIC METHODOLOGY.—The procedures described in clause (i) shall permit the Secretary to request that a specific methodology be used by the qualified entity. The qualified entity shall work with the Secretary to finalize the methodology to be used.

(E) USE OF ANALYSES.—The Secretary shall provide the analyses described in this paragraph, including the methods and results of such analyses, about a drug to the sponsor or sponsors of such drug.

(F) QUALIFIED ENTITIES.—

(i) IN GENERAL.—The Secretary shall enter into contracts with a sufficient number of qualified entities to develop and provide information to the Secretary in a timely manner.

(ii) QUALIFICATION.—The Secretary shall enter into a contract with an entity under clause (i) only if the Secretary determines that the entity has a significant presence in the United States and has one or more of the following qualifications:

(I) The research, statistical, epidemiologic, or clinical capability and expertise to conduct and complete the activities under this paragraph, including the capability and expertise to provide the Secretary de-identified data consistent with the requirements of this subsection.

(II) An information technology infrastructure in place to support electronic data and operational standards to provide security for such data.

(III) Experience with, and expertise on, the development of drug safety and effectiveness research using electronic population data.

(IV) An understanding of drug development or risk/benefit balancing in a clinical setting.

(V) Other expertise which the Secretary deems necessary to fulfill the activities under this paragraph.

(G) CONTRACT REQUIREMENTS.—Each contract with a qualified entity under subparagraph (F)(i) shall contain the following requirements:

(i) ENSURING PRIVACY.—The qualified entity shall ensure that the entity will not use data under this subsection in a manner that—

(I) violates the regulations promulgated under section 264(c) of the Health Insurance Portability and Accountability Act of 1996;

(II) violates sections 552 or 552a of title 5, United States Code, with regard to the privacy of individually-identifiable beneficiary health information; or

(III) discloses individually identifiable health information when presenting drug safety signals and trends or when responding to inquiries regarding drug safety signals and trends.

Nothing in this clause prohibits lawful disclosure for other purposes.

(ii) COMPONENT OF ANOTHER ORGANIZATION.—If a qualified entity is a component of another organization—

(I) the qualified entity shall establish appropriate security measures to maintain the confidentiality and privacy of such data; and

(II) the entity shall not make an unauthorized disclosure of such data to the other components of the organization in breach of such confidentiality and privacy requirement.

(iii) TERMINATION OR NONRENEWAL.—If a contract with a qualified entity under this subparagraph is terminated or not renewed, the following requirements shall apply:

(I) CONFIDENTIALITY AND PRIVACY PROTECTIONS.—The entity shall continue to comply with the confidentiality and privacy requirements under this paragraph with respect to all data disclosed to the entity.

(II) DISPOSITION OF DATA.—The entity shall return any data disclosed to such entity under this subsection to which it would not otherwise have access or, if returning the data is not practicable, destroy the data.

(H) COMPETITIVE PROCEDURES.—The Secretary shall use competitive procedures (as defined in section 4(5) of the Federal Procurement Policy Act) to enter into contracts under subparagraph (G).

(I) REVIEW OF CONTRACT IN THE EVENT OF A MERGER OR ACQUISITION.—The Secretary shall review the contract with a qualified entity under this paragraph in the event of a merger or acquisition of the entity in order to ensure

that the requirements under this paragraph will continue to be met.

(J) COORDINATION.—In carrying out this paragraph, the Secretary shall provide for appropriate communications to the public, scientific, public health, and medical communities, and other key stakeholders, and to the extent practicable shall coordinate with the activities of private entities, professional associations, or other entities that may have sources of drug safety data.

(5) The Secretary shall—

(A) conduct regular screenings of the Adverse Event Reporting System database and post a quarterly report on the Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk identified by Adverse Event Reporting System within the last quarter; and

(B) on an annual basis, review the entire backlog of postmarket safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments; and

(C) make available on the Internet website of the Food and Drug Administration—

(i) guidelines, developed with input from experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that detail best practices for drug safety surveillance using the Adverse Event Reporting System; and

(ii) criteria for public posting of adverse event signals.

(l)(1) Safety and effectiveness data and information which has been submitted in an application under subsection (b) for a drug and which has not previously been disclosed to the public shall be made available to the public, upon request, unless extraordinary circumstances are shown—

(A) if no work is being or will be undertaken to have the application approved,

(B) if the Secretary has determined that the application is not approvable and all legal appeals have been exhausted,

(C) if approval of the application under subsection (c) is withdrawn and all legal appeals have been exhausted,

(D) if the Secretary has determined that such drug is not a new drug, or

(E) upon the effective date of the approval of the first application under subsection (j) which refers to such drug or upon the date upon which the approval of an application under subsection (j) which refers to such drug could be made effective if such an application had been submitted.

(2) ACTION PACKAGE FOR APPROVAL.—

(A) ACTION PACKAGE.—The Secretary shall publish the action package for approval of an application under subsection (b) or section 351 of the Public Health Service Act on the Internet Web site of the Food and Drug Administration—

(i) not later than 30 days after the date of approval of such application for a drug no active ingredient (including

any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 351 of the Public Health Service Act; and

(ii) not later than 30 days after the third request for such action package for approval received under section 552 of title 5, United States Code, for any other drug.

(B) IMMEDIATE PUBLICATION OF SUMMARY REVIEW.—Notwithstanding subparagraph (A), the Secretary shall publish, on the Internet Web site of the Food and Drug Administration, the materials described in subparagraph (C)(iv) not later than 48 hours after the date of approval of the drug, except where such materials require redaction by the Secretary.

(C) CONTENTS.—An action package for approval of an application under subparagraph (A) shall be dated and shall include the following:

(i) Documents generated by the Food and Drug Administration related to review of the application.

(ii) Documents pertaining to the format and content of the application generated during drug development.

(iii) Labeling submitted by the applicant.

(iv) A summary review that documents conclusions from all reviewing disciplines about the drug, noting any critical issues and disagreements with the applicant and within the review team and how they were resolved, recommendations for action, and an explanation of any nonconcurrence with review conclusions.

(v) The Division Director and Office Director's decision document which includes—

(I) a brief statement of concurrence with the summary review;

(II) a separate review or addendum to the review if disagreeing with the summary review; and

(III) a separate review or addendum to the review to add further analysis.

(vi) Identification by name of each officer or employee of the Food and Drug Administration who—

(I) participated in the decision to approve the application; and

(II) consents to have his or her name included in the package.

(D) REVIEW.—A scientific review of an application is considered the work of the reviewer and shall not be altered by management or the reviewer once final.

(E) CONFIDENTIAL INFORMATION.—This paragraph does not authorize the disclosure of any trade secret, confidential commercial or financial information, or other matter listed in section 552(b) of title 5, United States Code.

(m) For purposes of this section, the term "patent" means a patent issued by the United States Patent and Trademark Office.

(n)(1) For the purpose of providing expert scientific advice and recommendations to the Secretary regarding a clinical investigation of a drug or the approval for marketing of a drug under section 505 or section 351 of the Public Health Service Act, the Secretary shall establish panels of experts or use panels of experts established be-

fore the date of enactment of the Food and Drug Administration Modernization Act of 1997, or both.

(2) The Secretary may delegate the appointment and oversight authority granted under section 1004 to a director of a center or successor entity within the Food and Drug Administration.

(3) The Secretary shall make appointments to each panel established under paragraph (1) so that each panel shall consist of—

(A) members who are qualified by training and experience to evaluate the safety and effectiveness of the drugs to be referred to the panel and who, to the extent feasible, possess skill and experience in the development, manufacture, or utilization of such drugs;

(B) members with diverse expertise in such fields as clinical and administrative medicine, pharmacy, pharmacology, pharmacoeconomics, biological and physical sciences, and other related professions;

(C) a representative of consumer interests, and a representative of interests of the drug manufacturing industry not directly affected by the matter to be brought before the panel; and

(D) two or more members who are specialists or have other expertise in the particular disease or condition for which the drug under review is proposed to be indicated.

Scientific, trade, and consumer organizations shall be afforded an opportunity to nominate individuals for appointment to the panels. No individual who is in the regular full-time employ of the United States and engaged in the administration of this Act may be a voting member of any panel. The Secretary shall designate one of the members of each panel to serve as chairman thereof.

(4) The Secretary shall, as appropriate, provide education and training to each new panel member before such member participates in a panel's activities, including education regarding requirements under this Act and related regulations of the Secretary, and the administrative processes and procedures related to panel meetings.

(5) Panel members (other than officers or employees of the United States), while attending meetings or conferences of a panel or otherwise engaged in its business, shall be entitled to receive compensation for each day so engaged, including traveltime, at rates to be fixed by the Secretary, but not to exceed the daily equivalent of the rate in effect for positions classified above grade GS–15 of the General Schedule. While serving away from their homes or regular places of business, panel members may be allowed travel expenses (including per diem in lieu of subsistence) as authorized by section 5703 of title 5, United States Code, for persons in the Government service employed intermittently.

(6) The Secretary shall ensure that scientific advisory panels meet regularly and at appropriate intervals so that any matter to be reviewed by such a panel can be presented to the panel not more than 60 days after the matter is ready for such review. Meetings of the panel may be held using electronic communication to convene the meetings.

(7) Within 90 days after a scientific advisory panel makes recommendations on any matter under its review, the Food and Drug Administration official responsible for the matter shall review the

conclusions and recommendations of the panel, and notify the affected persons of the final decision on the matter, or of the reasons that no such decision has been reached. Each such final decision shall be documented including the rationale for the decision.

(o) POSTMARKET STUDIES AND CLINICAL TRIALS; LABELING.—

(1) IN GENERAL.—A responsible person may not introduce or deliver for introduction into interstate commerce the new drug involved if the person is in violation of a requirement established under paragraph (3) or (4) with respect to the drug.

(2) DEFINITIONS.—For purposes of this subsection:

(A) RESPONSIBLE PERSON.—The term "responsible person" means a person who—

(i) has submitted to the Secretary a covered application that is pending; or

(ii) is the holder of an approved covered application.

(B) COVERED APPLICATION.—The term "covered application" means—

(i) an application under subsection (b) for a drug that is subject to section 503(b); and

(ii) an application under section 351 of the Public Health Service Act.

(C) NEW SAFETY INFORMATION; SERIOUS RISK.—The terms "new safety information", "serious risk", and "signal of a serious risk" have the meanings given such terms in section 505–1(b).

(3) STUDIES AND CLINICAL TRIALS.—

(A) IN GENERAL.—For any or all of the purposes specified in subparagraph (B), the Secretary may, subject to subparagraph (D), require a responsible person for a drug to conduct a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug, on the basis of scientific data deemed appropriate by the Secretary, including information regarding chemically-related or pharmacologically-related drugs.

(B) PURPOSES OF STUDY OR CLINICAL TRIAL.—The purposes referred to in this subparagraph with respect to a postapproval study or postapproval clinical trial are the following:

(i) To assess a known serious risk related to the use of the drug involved.

(ii) To assess signals of serious risk related to the use of the drug.

(iii) To identify an unexpected serious risk when available data indicates the potential for a serious risk.

(C) ESTABLISHMENT OF REQUIREMENT AFTER APPROVAL OF COVERED APPLICATION.—The Secretary may require a postapproval study or studies or postapproval clinical trial or trials for a drug for which an approved covered application is in effect as of the date on which the Secretary seeks to establish such requirement only if the Secretary becomes aware of new safety information.

(D) DETERMINATION BY SECRETARY.—

(i) POSTAPPROVAL STUDIES.—The Secretary may not require the responsible person to conduct a study

under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).

(ii) POSTAPPROVAL CLINICAL TRIALS.—The Secretary may not require the responsible person to conduct a clinical trial under this paragraph, unless the Secretary makes a determination that a postapproval study or studies will not be sufficient to meet the purposes set forth in subparagraph (B).

(E) NOTIFICATION; TIMETABLES; PERIODIC REPORTS.—

(i) NOTIFICATION.—The Secretary shall notify the responsible person regarding a requirement under this paragraph to conduct a postapproval study or clinical trial by the target dates for communication of feedback from the review team to the responsible person regarding proposed labeling and postmarketing study commitments as set forth in the letters described in section 101(c) of the Food and Drug Administration Amendments Act of 2007.

(ii) TIMETABLE; PERIODIC REPORTS.—For each study or clinical trial required to be conducted under this paragraph, the Secretary shall require that the responsible person submit a timetable for completion of the study or clinical trial. With respect to each study required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such study including whether any difficulties in completing the study have been encountered. With respect to each clinical trial required to be conducted under this paragraph or otherwise undertaken by the responsible person to investigate a safety issue, the Secretary shall require the responsible person to periodically report to the Secretary on the status of such clinical trial including whether enrollment has begun, the number of participants enrolled, the expected completion date, whether any difficulties completing the clinical trial have been encountered, and registration information with respect to the requirements under section 402(j) of the Public Health Service Act. If the responsible person fails to comply with such timetable or violates any other requirement of this subparagraph, the responsible person shall be considered in violation of this subsection, unless the responsible person demonstrates good cause for such noncompliance or such other violation. The Secretary shall determine what constitutes good cause under the preceding sentence.

(F) DISPUTE RESOLUTION.—The responsible person may appeal a requirement to conduct a study or clinical trial

under this paragraph using dispute resolution procedures established by the Secretary in regulation and guidance.

(4) SAFETY LABELING CHANGES REQUESTED BY SECRETARY.—

(A) NEW SAFETY OR NEW EFFECTIVENESS INFORMATION.—If the Secretary becomes aware of new information, including any new safety information or information related to reduced effectiveness, that the Secretary determines should be included in the labeling of the drug, the Secretary shall promptly notify the responsible person or, if the same drug approved under section 505(b) is not currently marketed, the holder of an approved application under 505(j).

(B) RESPONSE TO NOTIFICATION.—Following notification pursuant to subparagraph (A), the responsible person or the holder of the approved application under section 505(j) shall within 30 days—

(i) submit a supplement proposing changes to the approved labeling to reflect the new safety information, including changes to boxed warnings, contraindications, warnings, precautions, or adverse reactions, or new effectiveness information; or

(ii) notify the Secretary that the responsible person or the holder of the approved application under section 505(j) does not believe a labeling change is warranted and submit a statement detailing the reasons why such a change is not warranted.

(C) REVIEW.—Upon receipt of such supplement, the Secretary shall promptly review and act upon such supplement. If the Secretary disagrees with the proposed changes in the supplement or with the statement setting forth the reasons why no labeling change is necessary, the Secretary shall initiate discussions to reach agreement on whether the labeling for the drug should be modified to reflect the new safety or new effectiveness information, and if so, the contents of such labeling changes.

(D) DISCUSSIONS.—Such discussions shall not extend for more than 30 days after the response to the notification under subparagraph (B), unless the Secretary determines an extension of such discussion period is warranted.

(E) ORDER.—Within 15 days of the conclusion of the discussions under subparagraph (D), the Secretary may issue an order directing the responsible person or the holder of the approved application under section 505(j) to make such a labeling change as the Secretary deems appropriate to address the new safety or new effectiveness information. Within 15 days of such an order, the responsible person or the holder of the approved application under section 505(j) shall submit a supplement containing the labeling change.

(F) DISPUTE RESOLUTION.—Within 5 days of receiving an order under subparagraph (E), the responsible person or the holder of the approved application under section 505(j) may appeal using dispute resolution procedures established by the Secretary in regulation and guidance.

(G) VIOLATION.—If the responsible person or the holder of the approved application under section 505(j) has not

submitted a supplement within 15 days of the date of such order under subparagraph (E), and there is no appeal or dispute resolution proceeding pending, the responsible person or holder shall be considered to be in violation of this subsection. If at the conclusion of any dispute resolution procedures the Secretary determines that a supplement must be submitted and such a supplement is not submitted within 15 days of the date of that determination, the responsible person or holder shall be in violation of this subsection.

(H) PUBLIC HEALTH THREAT.—Notwithstanding subparagraphs (A) through (F), if the Secretary concludes that such a labeling change is necessary to protect the public health, the Secretary may accelerate the timelines in such subparagraphs.

(I) RULE OF CONSTRUCTION.—This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under section 505(j) to maintain its label in accordance with existing requirements, including subpart B of part 201 and sections 314.70 and 601.12 of title 21, Code of Federal Regulations (or any successor regulations).

(5) NON-DELEGATION.—Determinations by the Secretary under this subsection for a drug shall be made by individuals at or above the level of individuals empowered to approve a drug (such as division directors within the Center for Drug Evaluation and Research).

(p) RISK EVALUATION AND MITIGATION STRATEGY.—

(1) IN GENERAL.—A person may not introduce or deliver for introduction into interstate commerce a new drug if—

(A)(i) the application for such drug is approved under subsection (b) or (j) and is subject to section 503(b); or

(ii) the application for such drug is approved under section 351 of the Public Health Service Act; and

(B) a risk evaluation and mitigation strategy is required under section 505–1 with respect to the drug and the person fails to maintain compliance with the requirements of the approved strategy or with other requirements under section 505–1, including requirements regarding assessments of approved strategies.

(2) CERTAIN POSTMARKET STUDIES.—The failure to conduct a postmarket study under section 506, subpart H of part 314, or subpart E of part 601 of title 21, Code of Federal Regulations (or any successor regulations), is deemed to be a violation of paragraph (1).

(q) PETITIONS AND CIVIL ACTIONS REGARDING APPROVAL OF CERTAIN APPLICATIONS.—

(1) IN GENERAL.—

(A) DETERMINATION.—The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of this section or section 351(k) of the Public Health Service Act because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

(i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and

(ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.

(B) NOTIFICATION.—If the Secretary determines under subparagraph (A) that a delay is necessary with respect to an application, the Secretary shall provide to the applicant, not later than 30 days after making such determination, the following information:

(i) Notification of the fact that a determination under subparagraph (A) has been made.

(ii) If applicable, any clarification or additional data that the applicant should submit to the docket on the petition to allow the Secretary to review the petition promptly.

(iii) A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.

(C) FORMAT.—The information described in subparagraph (B) shall be conveyed via either, at the discretion of the Secretary—

(i) a document; or

(ii) a meeting with the applicant involved.

(D) PUBLIC DISCLOSURE.—Any information conveyed by the Secretary under subparagraph (C) shall be considered part of the application and shall be subject to the disclosure requirements applicable to information in such application.

(E) DENIAL BASED ON INTENT TO DELAY.—If the Secretary determines that a petition or a supplement to the petition was submitted with the primary purpose of delaying the approval of an application and the petition does not on its face raise valid scientific or regulatory issues, the Secretary may deny the petition at any point based on such determination. The Secretary may issue guidance to describe the factors that will be used to determine under this subparagraph whether a petition is submitted with the primary purpose of delaying the approval of an application.

(F) FINAL AGENCY ACTION.—The Secretary shall take final agency action on a petition not later than 150 days after the date on which the petition is submitted. The Secretary shall not extend such period for any reason, including—

(i) any determination made under subparagraph (A);

(ii) the submission of comments relating to the petition or supplemental information supplied by the petitioner; or

(iii) the consent of the petitioner.

(G) EXTENSION OF 30-MONTH PERIOD.—If the filing of an application resulted in first-applicant status under subsection (j)(5)(D)(i)(IV) and approval of the application was delayed because of a petition, the 30-month period under such subsection is deemed to be extended by a period of time equal to the period beginning on the date on which the Secretary received the petition and ending on the date of final agency action on the petition (inclusive of such beginning and ending dates), without regard to whether the Secretary grants, in whole or in part, or denies, in whole or in part, the petition.

(H) CERTIFICATION.—The Secretary shall not consider a petition for review unless the party submitting such petition does so in written form and the subject document is signed and contains the following certification: "I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.", with the date on which such information first became known to such party and the names of such persons or organizations inserted in the first and second blank space, respectively.

(I) VERIFICATION.—The Secretary shall not accept for review any supplemental information or comments on a petition unless the party submitting such information or comments does so in written form and the subject document is signed and contains the following verification: "I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me on or about _____. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: _____. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.", with the date on which such information first became known to the party and the names of such persons or organizations inserted in the first and second blank space, respectively.

(2) EXHAUSTION OF ADMINISTRATIVE REMEDIES.—

(A) FINAL AGENCY ACTION WITHIN 150 DAYS.—The Secretary shall be considered to have taken final agency action on a petition if—

(i) during the 150-day period referred to in paragraph (1)(F), the Secretary makes a final decision within the meaning of section 10.45(d) of title 21, Code of Federal Regulations (or any successor regulation); or

(ii) such period expires without the Secretary having made such a final decision.

(B) DISMISSAL OF CERTAIN CIVIL ACTIONS.—If a civil action is filed against the Secretary with respect to any issue raised in the petition before the Secretary has taken final agency action on the petition within the meaning of subparagraph (A), the court shall dismiss without prejudice the action for failure to exhaust administrative remedies.

(C) ADMINISTRATIVE RECORD.—For purposes of judicial review related to the approval of an application for which a petition under paragraph (1) was submitted, the administrative record regarding any issue raised by the petition shall include—

(i) the petition filed under paragraph (1) and any supplements and comments thereto;

(ii) the Secretary's response to such petition, if issued; and

(iii) other information, as designated by the Secretary, related to the Secretary's determinations regarding the issues raised in such petition, as long as the information was considered by the agency no later than the date of final agency action as defined under subparagraph (2)(A), and regardless of whether the Secretary responded to the petition at or before the approval of the application at issue in the petition.

(3) ANNUAL REPORT ON DELAYS IN APPROVALS PER PETITIONS.—The Secretary shall annually submit to the Congress a report that specifies—

(A) the number of applications that were approved during the preceding 12-month period;

(B) the number of such applications whose effective dates were delayed by petitions referred to in paragraph (1) during such period;

(C) the number of days by which such applications were so delayed; and

(D) the number of such petitions that were submitted during such period.

(4) EXCEPTIONS.—

(A) This subsection does not apply to—

(i) a petition that relates solely to the timing of the approval of an application pursuant to subsection (j)(5)(B)(iv); or

(ii) a petition that is made by the sponsor of an application and that seeks only to have the Secretary take or refrain from taking any form of action with respect to that application.

(B) Paragraph (2) does not apply to a petition addressing issues concerning an application submitted pursuant to section 351(k) of the Public Health Service Act.

(5) DEFINITIONS.—

(A) APPLICATION.—For purposes of this subsection, the term "application" means an application submitted under subsection (b)(2) or (j) of this section or section 351(k) of the Public Health Service Act.

(B) PETITION.—For purposes of this subsection, other than paragraph (1)(A)(i), the term "petition" means a request described in paragraph (1)(A)(i).

(r) POSTMARKET DRUG SAFETY INFORMATION FOR PATIENTS AND PROVIDERS.—

(1) ESTABLISHMENT.—Not later than 1 year after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, the Secretary shall improve the transparency of information about drugs and allow patients and health care providers better access to information about drugs by developing and maintaining an Internet Web site that—

(A) provides links to drug safety information listed in paragraph (2) for prescription drugs that are approved under this section or licensed under section 351 of the Public Health Service Act; and

(B) improves communication of drug safety information to patients and providers.

(2) INTERNET WEB SITE.—The Secretary shall carry out paragraph (1) by—

(A) developing and maintaining an accessible, consolidated Internet Web site with easily searchable drug safety information, including the information found on United States Government Internet Web sites, such as the United States National Library of Medicine's Daily Med and Medline Plus Web sites, in addition to other such Web sites maintained by the Secretary;

(B) ensuring that the information provided on the Internet Web site is comprehensive and includes, when available and appropriate—

(i) patient labeling and patient packaging inserts;

(ii) a link to a list of each drug, whether approved under this section or licensed under such section 351, for which a Medication Guide, as provided for under part 208 of title 21, Code of Federal Regulations (or any successor regulations), is required;

(iii) a link to the registry and results data bank provided for under subsections (i) and (j) of section 402 of the Public Health Service Act;

(iv) the most recent safety information and alerts issued by the Food and Drug Administration for drugs approved by the Secretary under this section, such as product recalls, warning letters, and import alerts;

(v) publicly available information about implemented RiskMAPs and risk evaluation and mitigation strategies under subsection (o);

(vi) guidance documents and regulations related to drug safety; and

(vii) other material determined appropriate by the Secretary;

(C) providing access to summaries of the assessed and aggregated data collected from the active surveillance infrastructure under subsection (k)(3) to provide information of known and serious side-effects for drugs approved under this section or licensed under such section 351;

(D) preparing and making publicly available on the Internet website established under paragraph (1) best practices for drug safety surveillance activities for drugs approved under this section or section 351 of the Public Health Service Act;

(E) enabling patients, providers, and drug sponsors to submit adverse event reports through the Internet Web site;

(F) providing educational materials for patients and providers about the appropriate means of disposing of expired, damaged, or unusable medications; and

(G) supporting initiatives that the Secretary determines to be useful to fulfill the purposes of the Internet Web site.

(3) POSTING OF DRUG LABELING.—The Secretary shall post on the Internet Web site established under paragraph (1) the approved professional labeling and any required patient labeling of a drug approved under this section or licensed under such section 351 not later than 21 days after the date the drug is approved or licensed, including in a supplemental application with respect to a labeling change.

(4) PRIVATE SECTOR RESOURCES.—To ensure development of the Internet Web site by the date described in paragraph (1), the Secretary may, on a temporary or permanent basis, implement systems or products developed by private entities.

(5) AUTHORITY FOR CONTRACTS.—The Secretary may enter into contracts with public and private entities to fulfill the requirements of this subsection.

(6) REVIEW.—The Advisory Committee on Risk Communication under section 567 shall, on a regular basis, perform a comprehensive review and evaluation of the types of risk communication information provided on the Internet Web site established under paragraph (1) and, through other means, shall identify, clarify, and define the purposes and types of information available to facilitate the efficient flow of information to patients and providers, and shall recommend ways for the Food and Drug Administration to work with outside entities to help facilitate the dispensing of risk communication information to patients and providers.

(s) REFERRAL TO ADVISORY COMMITTEE.—Prior to the approval of a drug no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under this section or section 351 of the Public Health Service Act, the Secretary shall—

(1) refer such drug to a Food and Drug Administration advisory committee for review at a meeting of such advisory committee; or

(2) if the Secretary does not refer such a drug to a Food and Drug Administration advisory committee prior to the approval

of the drug, provide in the action letter on the application for the drug a summary of the reasons why the Secretary did not refer the drug to an advisory committee prior to approval.

(t) DATABASE FOR AUTHORIZED GENERIC DRUGS.—

(1) IN GENERAL.—

(A) PUBLICATION.—The Commissioner shall—

(i) not later than 9 months after the date of the enactment of the Food and Drug Administration Amendments Act of 2007, publish a complete list on the Internet Web site of the Food and Drug Administration of all authorized generic drugs (including drug trade name, brand company manufacturer, and the date the authorized generic drug entered the market); and

(ii) update the list quarterly to include each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug during the preceding 3-month period.

(B) NOTIFICATION.—The Commissioner shall notify relevant Federal agencies, including the Centers for Medicare & Medicaid Services and the Federal Trade Commission, when the Commissioner first publishes the information described in subparagraph (A) that the information has been published and that the information will be updated quarterly.

(2) INCLUSION.—The Commissioner shall include in the list described in paragraph (1) each authorized generic drug included in an annual report submitted to the Secretary by the sponsor of a listed drug after January 1, 1999.

(3) AUTHORIZED GENERIC DRUG.—In this section, the term "authorized generic drug" means a listed drug (as that term is used in subsection (j)) that—

(A) has been approved under subsection (c); and

(B) is marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug.

(u) CERTAIN DRUGS CONTAINING SINGLE ENANTIOMERS.—

(1) IN GENERAL.—For purposes of subsections (c)(3)(E)(ii) and (j)(5)(F)(ii), if an application is submitted under subsection (b) for a non-racemic drug containing as an active ingredient (including any ester or salt of the active ingredient) a single enantiomer that is contained in a racemic drug approved in another application under subsection (b), the applicant may, in the application for such non-racemic drug, elect to have the single enantiomer not be considered the same active ingredient as that contained in the approved racemic drug, if—

(A)(i) the single enantiomer has not been previously approved except in the approved racemic drug; and

(ii) the application submitted under subsection (b) for such non-racemic drug—

(I) includes full reports of new clinical investigations (other than bioavailability studies)—

(aa) necessary for the approval of the application under subsections (c) and (d); and

(bb) conducted or sponsored by the applicant; and

(II) does not rely on any clinical investigations that are part of an application submitted under subsection (b) for approval of the approved racemic drug; and

(B) the application submitted under subsection (b) for such non-racemic drug is not submitted for approval of a condition of use—

(i) in a therapeutic category in which the approved racemic drug has been approved; or

(ii) for which any other enantiomer of the racemic drug has been approved.

(2) LIMITATION.—

(A) NO APPROVAL IN CERTAIN THERAPEUTIC CATEGORIES.—Until the date that is 10 years after the date of approval of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph, the Secretary shall not approve such non-racemic drug for any condition of use in the therapeutic category in which the racemic drug has been approved.

(B) LABELING.—If applicable, the labeling of a non-racemic drug described in paragraph (1) and with respect to which the applicant has made the election provided for by such paragraph shall include a statement that the non-racemic drug is not approved, and has not been shown to be safe and effective, for any condition of use of the racemic drug.

(3) DEFINITION.—

(A) IN GENERAL.—For purposes of this subsection, the term "therapeutic category" means a therapeutic category identified in the list developed by the United States Pharmacopeia pursuant to section 1860D–4(b)(3)(C)(ii) of the Social Security Act and as in effect on the date of the enactment of this subsection.

(B) PUBLICATION BY SECRETARY.—The Secretary shall publish the list described in subparagraph (A) and may amend such list by regulation.

(4) AVAILABILITY.—The election referred to in paragraph (1) may be made only in an application that is submitted to the Secretary after the date of the enactment of this subsection and before October 1, 2022.

(v) ANTIBIOTIC DRUGS SUBMITTED BEFORE NOVEMBER 21, 1997.—

(1) ANTIBIOTIC DRUGS APPROVED BEFORE NOVEMBER 21, 1997.—

(A) IN GENERAL.—Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv)

of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable.

(B) APPLICATION; ANTIBIOTIC DRUG DESCRIBED.—

(i) APPLICATION.—An application described in this clause is an application for marketing submitted under this section after the date of the enactment of this subsection in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) ANTIBIOTIC DRUG.—An antibiotic drug described in this clause is an antibiotic drug that was the subject of an application approved by the Secretary under section 507 of this Act (as in effect before November 21, 1997).

(2) ANTIBIOTIC DRUGS SUBMITTED BEFORE NOVEMBER 21, 1997, BUT NOT APPROVED.—

(A) IN GENERAL.—Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of a drug that is the subject of an application described in subparagraph (B)(i) may elect to be eligible for, with respect to the drug—

(i)(I) the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; and

(II) the 5-year exclusivity period referred to under clause (ii) of subsection (c)(3)(E) and under clause (ii) of subsection (j)(5)(F), subject to the requirements of such clauses, as applicable; or

(ii) a patent term extension under section 156 of title 35, United States Code, subject to the requirements of such section.

(B) APPLICATION; ANTIBIOTIC DRUG DESCRIBED.—

(i) APPLICATION.—An application described in this clause is an application for marketing submitted under this section after the date of the enactment of this subsection in which the drug that is the subject of the application contains an antibiotic drug described in clause (ii).

(ii) ANTIBIOTIC DRUG.—An antibiotic drug described in this clause is an antibiotic drug that was the subject of 1 or more applications received by the Secretary under section 507 of this Act (as in effect before November 21, 1997), none of which was approved by the Secretary under such section.

(3) LIMITATIONS.—

(A) EXCLUSIVITIES AND EXTENSIONS.—Paragraphs (1)(A) and (2)(A) shall not be construed to entitle a drug that is the subject of an approved application described in subparagraphs (1)(B)(i) or (2)(B)(i), as applicable, to any market exclusivities or patent extensions other than those exclusivities or extensions described in paragraph (1)(A) or (2)(A).

(B) CONDITIONS OF USE.—Paragraphs (1)(A) and (2)(A)(i) shall not apply to any condition of use for which the drug referred to in subparagraph (1)(B)(i) or (2)(B)(i), as applicable, was approved before the date of the enactment of this subsection.

(4) APPLICATION OF CERTAIN PROVISIONS.—Notwithstanding section 125, or any other provision, of the Food and Drug Administration Modernization Act of 1997, or any other provision of law, and subject to the limitations in paragraphs (1), (2), and (3), the provisions of the Drug Price Competition and Patent Term Restoration Act of 1984 shall apply to any drug subject to paragraph (1) or any drug with respect to which an election is made under paragraph (2)(A).

(w) DEADLINE FOR DETERMINATION ON CERTAIN PETITIONS.—The Secretary shall issue a final, substantive determination on a petition submitted pursuant to subsection (b) of section 314.161 of title 21, Code of Federal Regulations (or any successor regulations), no later than 270 days after the date the petition is submitted.

(x) DATE OF APPROVAL IN THE CASE OF RECOMMENDED CONTROLS UNDER THE CSA.—

(1) IN GENERAL.—In the case of an application under subsection (b) with respect to a drug for which the Secretary provides notice to the sponsor that the Secretary intends to issue a scientific and medical evaluation and recommend controls under the Controlled Substances Act, approval of such application shall not take effect until the interim final rule controlling the drug is issued in accordance with section 201(j) of the Controlled Substances Act.

(2) DATE OF APPROVAL.—For purposes of this section, with respect to an application described in paragraph (1), the term "date of approval" shall mean the later of—

(A) the date an application under subsection (b) is approved under subsection (c); or

(B) the date of issuance of the interim final rule controlling the drug.

(y) CONTRAST AGENTS INTENDED FOR USE WITH APPLICABLE MEDICAL IMAGING DEVICES.—

(1) IN GENERAL.—The sponsor of a contrast agent for which an application has been approved under this section may submit a supplement to the application seeking approval for a new use following the authorization of a premarket submission for an applicable medical imaging device for that use with the contrast agent pursuant to section 520(p)(1).

(2) REVIEW OF SUPPLEMENT.—In reviewing a supplement submitted under this subsection, the agency center charged with the premarket review of drugs may—

(A) consult with the center charged with the premarket review of devices; and

(B) review information and data submitted to the Secretary by the sponsor of an applicable medical imaging device pursuant to section 515, 510(k), or 513(f)(2) so long as the sponsor of such applicable medical imaging device has provided to the sponsor of the contrast agent a right of reference.

(3) DEFINITIONS.—For purposes of this subsection—

(A) the term "new use" means a use of a contrast agent that is described in the approved labeling of an applicable medical imaging device described in section 520(p), but that is not described in the approved labeling of the contrast agent; and

(B) the terms "applicable medical imaging device" and "contrast agent" have the meanings given such terms in section 520(p).

* * * * * * *

○

EXHIBIT H

method

1

: a procedure or process for attaining an object: such as

a(1)
: a systematic procedure, technique, or mode of inquiry employed by or proper to a particular discipline or art

(2)
: a systematic plan followed in presenting material for instruction
the lecture method

b(1)
: a way, technique, or process of or for doing something
often slow in their business methods – T. R. Ybarra
(2)
: a body of skills or techniques
in the art of the novel, heavily armed with method – J. D. Scott
2

: a discipline that deals with the principles and techniques of scientific inquiry

3

a
: orderly arrangement, development, or classification : PLAN

The book is completely lacking in method.

b
: the habitual practice of orderliness and regularity
time enough to do everything if only you used method – Angela Thirkell
4

capitalized **:** a dramatic technique by which an actor seeks to gain complete identification with the inner personality of the character being portrayed

Synonyms

See all Synonyms & Antonyms in Thesaurus ›
Choose the Right Synonym for *method*

method, mode, manner, way, fashion, system mean the means taken or procedure followed in achieving an end.

method implies an orderly logical arrangement usually in steps.

effective teaching *methods*

mode implies an order or course followed by custom, tradition, or personal preference.

the preferred *mode* of transportation

manner is close to mode but may imply a procedure or method that is individual or distinctive.

an odd *manner* of conducting

way is very general and may be used for any of the preceding words.

has her own *way* of doing things

fashion may suggest a peculiar or characteristic way of doing something.

rushing about in his typical *fashion*

system suggests a fully developed or carefully formulated method often emphasizing rational orderliness.

a filing *system*

Example Sentences

He claims to have developed a new *method* for growing tomatoes.

Their teaching *method* tries to adapt lessons to each student.

We need to adopt more modern *methods* of doing things.

Recent Examples on the Web Each *method* can be touched up, year after year, for a flawless finish. – Emily Vanschmus, *Better Homes & Gardens*, 15 Nov. 2022 But Levin and Gambaryan's *method* could somehow obtain those identifiers. – *WIRED*, 15 Nov. 2022 Unfortunately, the scientist's ground-breaking *method* for becoming invisible is slowly driving him insane. – Steven Thrash, *EW.com*, 14 Nov. 2022 Dillon added that efforts to put pressure on Musk are in progress, including advertisers and activists who are influencing them, but argued Musk's verification *method* is one way to combat revenue losses. – Taylor Penley, *Fox News*, 14 Nov. 2022 The before and after *method* is just that - a comparison of the value of the land before the easement was placed on it, compared with the value of the land after. – Guinevere Moore, *Forbes*, 11 Nov. 2022 Subsequently, make an initial deposit of at least $5 using any secure deposit *method* DraftKings offers. – *cleveland*, 10 Nov. 2022 The novelty in this case was the combination of *method* and medication. – Andrew Joseph, *STAT*, 9 Nov. 2022 For anyone who gains access to your data under that encryption *method*, it's like breaking into a jewelry store and being unable to steal anything, Schiappa says. – Nick Rockel, *Fortune*, 9 Nov. 2022 See More

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Word History

Etymology

Middle English, prescribed treatment, from Latin *methodus*, from Greek *methodos*, from *meta-* + *hodos* way

First Known Use

15th century, in the meaning defined at sense 1

Time Traveler

The first known use of *method* was in the 15th century
See more words from the same century

Phrases Containing *method*

(a) method in/to one's madness

rhythm method

method of fluxions

the scientific method

scientific method

Stanislavski method

(a) method in/to one's madness

rhythm method

method of fluxions

the scientific method

scientific method

Stanislavski method

Dictionary Entries Near *method*

methobromide

method

methodical

See More Nearby Entries ›

Cite this Entry

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Kids Definition

method

noun

meth·od ˈmeth-əd

1

: a way, plan, or procedure for doing something

2

: orderly arrangement

Medical Definition

method

noun

meth·od ˈmeth-əd

: a procedure or process for attaining an object: as

a
: a systematic procedure, technique, or mode of inquiry employed by or proper to a particular discipline → see SCIENTIFIC METHOD
b
: a way, technique, or process of or for doing something

More from Merriam-Webster on *method*

Nglish: Translation of *method* for Spanish Speakers

Britannica English: Translation of *method* for Arabic Speakers

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WORD OF THE DAY

See Definitions and Examples »

- 

- I went to the _____ store to buy a birthday card.

  stationery stationary

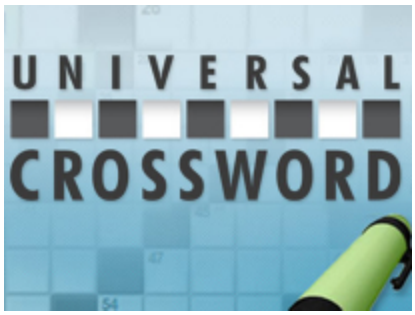

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EXHIBIT I

system

1

: a regularly interacting or interdependent group of items forming a unified whole
a number system

: such as
a(1)
: a group of interacting bodies under the influence of related forces
a gravitational system

(2)
: an assemblage of substances that is in or tends to equilibrium
a thermodynamic system

b(1)
: a group of body organs that together perform one or more vital functions
the digestive system

(2)
: the body considered as a functional unit

c
: a group of related natural objects or forces
a river system

d

: a group of devices or artificial objects or an organization forming a network especially for distributing something or serving a common purpose
a telephone system

a heating system

a highway system

a computer system

e
: a major division of rocks usually larger than a series and including all formed during a period or era

f
: a form of social, economic, or political organization or practice
the capitalist system

2

: an organized set of doctrines, ideas, or principles usually intended to explain the arrangement or working of a systematic whole
the Newtonian system of mechanics

3

a
: an organized or established procedure
the touch system of typing

b
: a manner of classifying, symbolizing, or schematizing
a taxonomic system

the decimal system

4

: harmonious arrangement or pattern : ORDER
bring system out of confusion – Ellen Glasgow
5

: an organized society or social situation regarded as stultifying or oppressive : ESTABLISHMENT sense 2 → —usually used with *the*
systemless ˈsi-stəm-ləs adjective

Synonyms

- complex
- network

See all Synonyms & Antonyms in Thesaurus ›
Choose the Right Synonym for *system*

method, mode, manner, way, fashion, system mean the means taken or procedure followed in achieving an end.

method implies an orderly logical arrangement usually in steps.

effective teaching *methods*

mode implies an order or course followed by custom, tradition, or personal preference.

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has her own *way* of doing things

fashion may suggest a peculiar or characteristic way of doing something.

rushing about in his typical *fashion*

system suggests a fully developed or carefully formulated method often emphasizing rational orderliness.

a filing *system*

Example Sentences

The players like the coach's *system*.

Under the new *system*, students will have to pass an exam to graduate.

She devised a new filing *system*.

We need a better *system* for handling incoming e-mail.

Recent Examples on the Web The workings of the criminal justice *system* were never Dead to Me's strong suit or main concern, and the investigator characters don't get much in the way of a send-off. – *Time*, 18 Nov. 2022 The city plans to launch two pilot programs in 2023 aimed at youth groups, including those transitioning out of the foster care *system*. – Christian Martinezstaff Writer, *Los Angeles Times*, 18 Nov. 2022 There's absolutely no need to throw every border asylum claim into the drawn-out and adversarial arena of a court *system*. – Felipe De La Hoz, *The New Republic*, 18 Nov. 2022 The stadium's dual arches remained intact and were joined by a wide canopy to support the integration of the cooling *system*. – Tim Newcomb, *Popular Mechanics*, 18 Nov. 2022 During the construction of the interstate highway *system* from the 1950s to the 1970s, engineers slammed highways through urban areas, often creating racial barriers between neighborhoods. – Steven Litt, *cleveland*, 17 Nov. 2022 If Ukraine did inadvertently shoot an SA-10 missile deep into Polish territory, this would not be the first case of a Soviet-era missile defense *system* missing its mark. – John Hudson, *Washington Post*, 17 Nov. 2022 Sarafin ticked off all of the launch accomplishments including all of the separation events for the rocket including the boosters, fairings, jettison of the launch abort *system*, shutdown the four RS-25 engines and jettison of the core stage. – Richard Tribou, *Orlando Sentinel*, 17 Nov. 2022 Another worry is the blow to the credibility of the financial *system*. – *Arkansas Online*, 17 Nov. 2022 See More

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Word History

Etymology

Late Latin *systemat-, systema*, from Greek *systēmat-, systēma*, from *synistanai* to combine, from *syn-* + *histanai* to cause to stand — more at stand

First Known Use

circa 1638, in the meaning defined at sense 1

Time Traveler

The first known use of *system* was circa 1638
See more words from the same year

Phrases Containing *system*

binary system

a shock to the/someone's system

buddy system

buck the system

central nervous system

case system

decimal system

English system

get it out of one's system

haversian system

honor system

immune system

life-support system

limbic system

merit system

metric system

operating system

mononuclear phagocyte system

PA system

peripheral nervous system

portal system

profit system

respiratory system

reproductive system

sprinkler system

spoils system

sympathetic nervous system

support system

star system

the buddy system

truck system

the system

circulatory system

autonomic nervous system

Bertillon system

expert system

public address system

intercommunication system

inter-system

reticuloendothelial system

digestive system

ABO system

sound system

nervous system

lymphatic system

clipper system

foster system

touch system

the metric system

parasympathetic nervous system

water-vascular system

sub-system

solar system

wall system

tetragonal system

See More

binary system

a shock to the/someone's system

buddy system

buck the system

central nervous system

case system

decimal system

English system

get it out of one's system

haversian system

honor system

immune system

life-support system

limbic system

merit system

metric system

operating system

mononuclear phagocyte system

PA system

peripheral nervous system

portal system

profit system

respiratory system

reproductive system

sprinkler system

spoils system

sympathetic nervous system

support system

star system

the buddy system

truck system

the system

circulatory system

autonomic nervous system

Bertillon system

expert system

public address system

intercommunication system

inter-system

reticuloendothelial system

digestive system

ABO system

sound system

nervous system

lymphatic system

clipper system

foster system

touch system

the metric system

parasympathetic nervous system

water-vascular system

sub-system

solar system

wall system

tetragonal system

See More

Dictionary Entries Near *system*

systaltic

system

systematic

See More Nearby Entries ›

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Kids Definition

system

noun

sys·tem ˈsis-təm

1

a
: a group of objects or units combined to form a whole and to move or work together
the railroad *system*

a park *system*

b
: a group of bodily organs that together carry on one or more vital functions
the digestive *system*

c

: the body considered as a functional unit
a *system* weakened by disease

d
: an orderly plan or method of governing or arranging
a democratic *system* of government

e
: a major division of rocks usually larger than a series and including all formed during a period or era

2

a
: a set of ideas or statements that explains the order or functioning of a whole

b
: a method of classifying, representing, or arranging
a decimal *system* of numbers

systemless -ləs adjective

Medical Definition

system

noun

sys·tem ˈsis-təm

1

a
: a group of body organs or structures that together perform one or more vital functions → see CIRCULATORY SYSTEM, DIGESTIVE SYSTEM, ENDOCRINE SYSTEM, LIMBIC SYSTEM, NERVOUS SYSTEM, REPRODUCTIVE SYSTEM, RESPIRATORY SYSTEM
b
: the body considered as a functional unit

2

: a manner of classifying, symbolizing, or schematizing

a taxonomic system

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Britannica English: Translation of *system* for Arabic Speakers

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- Namesake of the *leotard*, Jules Léotard had what profession?
- Surgeon Acrobat
- Firefighter Judge

You know what it looks like… but what is it called?

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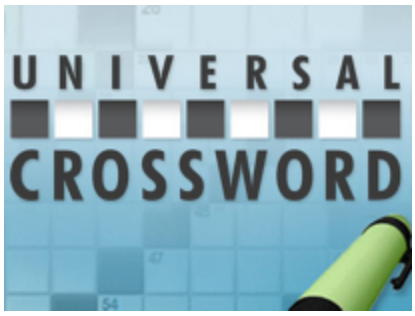

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