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November 17, 2017

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2017-N-3615: Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access; Public Meeting; Request for Comments

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to the Food and Drug Administration's (FDA's or the Agency's) request for comments on "Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access."[1] PhRMA represents the country's leading innovative biopharmaceutical research and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures, with members investing an estimated $65.5 billion in 2016 in the discovery and development of new medicines.

PhRMA participated in the public meeting and is pleased to supplement our comments. PhRMA believes there have been successes in the implementation of Hatch-Waxman over the last three decades, but there have also been discrete issues that have arisen that FDA should consider addressing when developing its policies in this area.

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments (or simply Hatch-Waxman), was intended both to increase access to generic medicines and to preserve incentives for innovation. As such, in considering the "balance between innovation and access," FDA needs to consider the impact on incentives for innovation, as well as on the availability of lower-cost generic versions of innovative medicines.

Intellectual property (IP) protections are a critical incentive for innovation. IP protections are the lifeblood of innovation in pharmaceuticals, given the unique attributes of the pharmaceutical R&D process, which is lengthy, costly, and uncertain. It takes on average 10 to 15 years and costs $2.6 billion on average to develop a new medicine.[2] Protocol design for clinical trials has increased in complexity, which demands the investment of more sponsor

[1] 82 Fed. Reg. 28493 (June 22, 2017).

[2] DiMasi JA, Grabowski HG, Hansen RW. *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs.* J Health Econ. 2016;47:20-33 (DiMasi 2016).

resources and can present challenges for patient enrollment and retention.[3] IP protections, including both patents and statutory exclusivity protections such as Hatch-Waxman five- and three-year exclusivity protections, are key to supporting continued future innovation in the long term. They are based on the concept of providing exclusive marketing periods for a set period of time as an incentive to support the substantial R&D efforts required for discovering and developing new and improved medicines. These incentives are particularly critical given the need to account for the many R&D failures—only 12% of compounds reaching clinical trials are ultimately approved.[4]

PhRMA supports the important role of generic drug products. The natural evolution of medicines is that, after an innovator undertakes the time-consuming, uncertain, and expensive development process and obtains FDA approval, it enjoys an appropriate period of IP protections, including both data protection and patent protections, following which a generic version can be approved. Indeed, this is the very cycle that Hatch-Waxman was intended to encourage.

Hatch-Waxman has fostered competition through the timely entry of generic drugs. For example:

- As FDA officials have recognized, 90% of all prescriptions in the United States are filled with generic products.[5]
- For brand medicines facing generic entry in 2013-2014, generics captured an average of 93% of the market (by volume) within a year of entry.[6]
- This competitive dynamic is expected to continue in the years ahead.[7]
- The patent challenge procedures of Hatch-Waxman are robust. Multiple generic applicants typically challenge listed patents as soon as they are able to do so.

On the other hand, FDA must also consider the Hatch-Waxman Amendments from the perspective of incentives for innovation. Incentives for innovation support competition. The introduction of innovative therapies provides patients with new treatment options and leads to competition where there are multiple alternatives in a given therapeutic class. These incentives must be considered when weighing the Hatch-Waxman balance. From an IP perspective, Hatch-Waxman includes not just the patent term restoration provisions, but also important patent protections in the context of patent challenges by generic companies, as well as the data protection provisions for new chemical entities (five years) and new clinical investigations leading to new drug products or new uses (three years). PhRMA believes that there are certain areas where incentives for innovation may be insufficient.

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[3] *See* Getz KA, Campo RA. *New Benchmarks Characterizing Growth in Protocol Design Complexity*. Therapeutic Innovation & Regul Sci. 2017.

[4] DiMasi 2016.

[5] IMS Institute for Healthcare Informatics, *Medicines Use and Spending in the U.S. A Review of 2016 and Outlook to 2021* (May 2017).

[6] Grabowski H, Long G, Mortimer R, Boyo A. *Updated Trends in US Brand-Name and Generic Drug Competition*. J Med Economics. 2016;19(9):836-844 (Grabowski 2016).

[7] QuintilesIMS Institute, *Outlook for Global Medicines Through 2021: Balancing Cost and Value* (Dec. 2016).

With respect to data protection, Hatch-Waxman's incentives for innovation have not proven to be as robust as intended. The existing five-year new chemical entity data protection period that begins upon FDA approval of the new drug does not alone sufficiently reward investment in small molecule drugs,[8] particularly for the novel and complex drugs currently under development.[9] It provides less protection than in other developed countries and regions—particularly the European Union, where an innovative product receives eight years of data exclusivity upon approval followed by an additional two years of marketing exclusivity that can be extended by one additional year if, during the first eight years, the sponsor obtains a marketing authorization for an applicable new indication.[10]

Similarly, the incentives provided by three-year exclusivity have been significantly weakened and do not sufficiently support the types of innovations eligible for such exclusivity (e.g., new uses of approved products). For example, where a therapeutically equivalent generic product's labeling does not include one of the reference listed drug's (RLD's) indications protected by Hatch-Waxman three-year exclusivity, pharmacists will still automatically substitute the generic version. This is the case even where the patient is taking the drug for treatment of the protected indication, thereby undermining the incentive for the innovator to obtain approval of a new indication.[11] Given the substantial investment required for the studies undertaken to obtain the approvals that lead to three-year exclusivity and the benefit to the public health from such investment, we believe that FDA can, and should, take additional steps to ensure the proper balance between innovation and competition in this context.[12]

When patents are considered, there are also areas where incentives for innovation have weakened over time. The patent challenge procedure under Hatch-Waxman has proven to be a robust means for generic applicants to attempt to market generic versions prior to expiration of listed patents. Over the thirty-three years since enactment of Hatch-Waxman, patent challenges from generic manufacturers (in the form of paragraph IV certifications) have been filed more frequently and earlier in the brand-name drug life cycle, with many as soon as possible under the statute— in the case of a new chemical entity, as early as four years after approval.[13]

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[8] Data protection is particularly important where patent protection is not available for a product or patent protection has expired or will soon expire.

[9] Instead, U.S. law provides more substantial incentives for development of new biologics in the Biologics Price Competition and Innovation Act (BPCIA), with a longer data protection period that provides more certainty for innovators and more appropriately rewards innovation. *See* Public Health Service Act § 351(k)(7).

[10] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use, Art. 10.1.

[11] *See, e.g.*, Letter from Janet Woodcock, M.D., FDA, to Ernest Lengle, Ph.D., Watson Labs., Inc., re: Docket No. FDA-2008-P-0069, at 12 (July 28, 2008) ("[T]he fact that state substitution laws may result in the dispensing of generic irinotecan for the protected combination-use provides no basis for denying approval of an irinotecan ANDA.").

[12] For example, we understand that a recent FDA decision authorized a follow-on product manufacturer to promote its drug product for a condition of use *not* in the follow-on drug product's labeling because of three-year exclusivity. *See, e.g.*, Kurt Karst, FDA Law Blog, *Should Free Speech Protections Include an Exception for Exclusivity-Protected Information?* (Jun. 8, 2017), http://bit.ly/2sQJ6uL. This approach effectively renders three-year exclusivity worthless in such situations. As PhRMA has noted in other comments submitted to FDA, in this special circumstance—where there is an exclusivity-protected supplemental use and an unprotected prior use for which a follow-on product has been approved—restricting communications about the exclusivity-protected use would directly advance the government's legitimate interest in preserving incentives for innovation, and no less restrictive alternative would be available. *See* PhRMA, Comments to Docket No. FDA-2016-N-1149, Section III.G (Apr. 19, 2017).

[13] Grabowski 2016.

The statutory exclusivity and patent provisions collectively provide less incentive for innovation than one might expect. The market exclusivity period before first generic entry for small molecules has declined over time such that brand medicines have faced generic competition at just over twelve years after brand launch, even though the basic patent term is twenty years.[14] Combined with the uncertainties of the patent system, due in part to Supreme Court rulings on patentability[15] and increased use of the *inter partes* review (IPR) process at the Patent and Trademark Office—with some petitions filed even before the four-year mark after approval of the innovator's new chemical entity—the current IP framework can create challenges for innovative companies looking to develop new products. Efforts to further limit patent settlements concerning generic drugs would further reduce the value of patent protections and create additional challenges for companies.

On the other hand, there are areas where generic competition could be enhanced without reducing incentives for innovation. FDA review times for generic drug applications also have been an issue noted by policy makers. PhRMA supports FDA's work to streamline and expedite the generic drug approval process, especially where there is no IP remaining for the innovator product. In particular, we support FDA's steps to foster preparation of more high-quality generic applications to reduce the number of review cycles for these applications.

Further, as FDA recognizes in the Federal Register notice, there are certain circumstances where existing incentives might be insufficient to spur generic development. PhRMA applauds FDA's recent actions to help address this issue—including by publishing a list of off-patent, off-exclusivity drugs without approved generics and updating its Manual of Policies and Procedures (MaPP) to provide for expedited review of certain generic applications.[16] PhRMA also applauds the provisions of the FDA Reauthorization Act of 2017 (FDARA) and the commitment letter accompanying the Generic Drug User Fee Amendments of 2017 (GDUFA II) in Title III of FDARA that provide enhancements to the generic drug approval process in these situations and codify FDA's publication of the list, as well as the FDARA provisions that seek to encourage and expedite the development and review of applications for competitive generic therapies.[17] PhRMA believes that additional steps could be taken to further promote the development of generic versions of off-patent, off-exclusivity drugs that do not have generic competition.

In addition to these general comments, below PhRMA addresses specific issues relating to citizen petitions, risk evaluation and mitigation strategies (REMS), post-approval reformulations and other changes, and product appearance raised in the Federal Register notice and/or the public meeting.

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[14] *Id*. at 843.

[15] Rulings by the Court of Appeals for the Federal Circuit, such as the double patenting decision in *Gilead Sciences, Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014), *cert. denied* 135 S. Ct. 1530 (2015), have also increased uncertainty as to the degree of patent protection available for companies.

[16] *See* FDA, *List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic*, https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/UCM564441.pdf; FDA, Center for Drug Evaluation and Research (CDER), MAPP 5240.3 Rev. 4, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements* (Nov. 9, 2017).

[17] *See* FDARA, Pub. L. No. 115-52, §§ 801, 803, 808, 131 Stat. 1005, 1068-71, 1074-75 (2017); FDA, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022*, https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

I. Citizen Petitions

FDA requested stakeholder input on "[h]ow . . . the balance struck in the Hatch-Waxman Amendments [has] been affected by practices and trends relating to . . . [o]ther regulatory processes, including the citizen petition process."[18] As discussed below, the citizen petition process has served, and continues to serve, as an important avenue for raising critical scientific, policy, and legal issues for FDA's consideration and fostering robust public dialogue about them. Claims that innovator citizen petitions are frivolous and delay generic entry are based on flawed data and incomplete analysis, and the agency has the authority to deny, at any time, any petition that "was submitted with the primary purpose of delaying the approval of an application and . . . does not on its face raise valid scientific or regulatory issues."[19] Further, claims that innovators file "serial" petitions with the purpose of delaying generic entry are misplaced, and PhRMA recommends that FDA reconsider its policy of denying petitions without ever ruling on the merits and enable all petitioners to obtain a substantive response to their petitions without filing multiple petitions. Finally, FDA should not adopt a proposal under which certain petitions would not receive a full review based on the timing of their filing, as the innovator might not have received notice of the factual basis for the petition until just before that time.

A. Citizen petitions play a critical role for both FDA and the public.

The citizen petition process promotes public exchange of information and ideas about scientific, legal, and regulatory matters, which is critical to achieving the agency's public health mission. Through petitions, FDA receives valuable input reflecting various perspectives, and, through comments on petitions, the public may engage in the agency's deliberative process. Indeed, Commissioner Gottlieb has recognized that "[c]itizen petitions often raise relevant issues and provide useful information for FDA. They provide interested parties with a vehicle to bring their concerns before FDA, and are therefore an important element of good governance and public accountability."[20] Further, the citizen petition procedure implements constitutional requirements: as FDA has acknowledged, "the First Amendment to the Constitution explicitly recognizes the right of the people to petition the government for a redress of grievances."[21]

Moreover, under the Federal Food, Drug, and Cosmetic Act (FDCA) and agency guidance, citizen petitions are the only permissible mechanism for innovators to raise certain issues and concerns with FDA, including concerns regarding key safety and effectiveness standards for generic drugs. As interpreted by FDA, section 505(q) of the FDCA requires that requests to take any administrative action that could, "under any reasonable theory," delay approval of a pending abbreviated application be submitted in a citizen petition.[22] For

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[18] 82 Fed. Reg. at 28,495 (June 22, 2017).

[19] FDCA § 505(q)(1)(E).

[20] Statement of Scott Gottlieb, M.D., Commissioner of Food and Drugs, before the Subcommittee on Regulatory Reform, Commercial and Antitrust Law, U.S. House Committee on the Judiciary, at 9 (July 27, 2017) (Gottlieb Statement).

[21] FDA, *Administrative Practices and Procedures*, 40 Fed. Reg. 40,682, 40,686 (Sept. 3, 1975) (citing 5 U.S.C. § 553(d)); *see also United Mine Workers of Am. v. Ill. State Bar Ass'n*, 389 U.S. 217, 222 (1967) (describing "the right[] . . . to petition for a redress of grievances [as] among the most precious of the liberties safeguarded by the Bill of Rights.").

[22] *See* FDCA § 505(q)(1)(A); FDA, Guidance for Industry, *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*, at 6, 8 (Rev. 1, Nov. 2014) (505(q) Guidance).

submissions about an abbreviated application that are *not* subject to section 505(q), FDA guidance stipulates that they "are appropriately submitted through the petition process . . . rather than as correspondence to the [application] or another process."[23] Due to their extensive knowledge and experience with the drugs in question, innovators have important contributions to make to FDA's consideration of issues regarding the safety and other standards for approval of abbreviated applications. Ensuring that the citizen petition procedure remains available for innovators to raise concerns relating to abbreviated applications therefore is in the public health interest.

B. Claims that nearly all innovator citizen petitions lack merit are based on flawed metrics and incomplete analysis.

Relying upon data purportedly showing that FDA denies a high percentage of innovator citizen petitions, some observers claim that innovators file frivolous petitions to delay generic entry.[24] The underlying studies did not attempt to assess the strength of these petitions on the merits, however. Further, these claims are based on data that count only the raw number of petitions denied—including petitions that FDA *denied without comment on their merits*.

As FDA has explained, it routinely issues such non-substantive, procedural denials due to the agency's approach to implementing section 505(q):

> [W]e do not interpret section 505(q) to require a substantive final Agency decision within 150 days on the approvability of a specific aspect of a pending application when a final decision on the approvability of the application as a whole has not yet been made and when to render such a decision could deprive an applicant of procedural rights established by statute and regulations. In such a situation, we would expect to deny a petition without comment on the substantive approval issue.[25]

These non-substantive denials typically state that "the Petition is denied without comment on whether we will take the actions you request." These responses therefore provide no information about FDA's views on the strength of the petition's arguments. Nevertheless, neither FDA's data on responses to citizen petitions[26] nor the studies cited to support claims

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[23] 505(q) Guidance, at 6.

[24] *See, e.g.*, Feldman R, Wang C. *A Citizen's Pathway Gone Astray — Delaying Competition from Generic Drugs.* N Engl J Med. 2017 Apr 20;376(16):1499-1501; Robin Feldman et al., *Empirical Evidence of Drug Pricing Games – A Citizen's Pathway Gone Astray*, 20 STAN. TECH. L. REV. 39 (2017) (Feldman 2017); Michael A. Carrier & Carl J. Minniti III, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. U. L. REV. 305 (2016), at 351-52 (Carrier 2016) ("[T]he FDA den[ies] more than 9 out of every 10 petitions . . . . In short, . . . citizen petitions continue to play an increasingly important role in delaying generic competition."); Robin Feldman & Evan Frondorf, *Drug Wars: A New Generation of Generic Pharmaceutical Delay*, 53 HARV. J. LEG. 499 (2016); Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249 (2012) (Carrier 2012).

[25] 505(q) Guidance, at 13-14.

[26] *See, e.g.*, FDA, *Eighth Annual Report on Delays in Approvals of Applications Related to Citizen Petitions and Petitions for Stay of Agency Action for Fiscal Year 2015*, at 7 (July 2016) (noting that the category for "denied" petitions "includes instances where FDA issued a denial without comment on the substance of one or more of the requests.") (Eighth Annual Report).

that innovators' petitions generally are frivolous distinguish between these non-substantive denials and denials of citizen petitions on the merits.[27]

Indeed, non-substantive denials as described above account for a significant proportion of citizen petition responses that FDA, and these studies, characterize as "denials." For example, for section 505(q) petitions to which FDA responded in 2015, eight of FDA's sixteen "denials" were non-substantive denials.[28] Of FDA's twelve responses to section 505(q) petitions issued in 2016, four were at least in part non-substantive denials, and two of the substantive responses stated that they granted the underlying petition in part. Similarly, of the twenty petition responses issued in 2017 through September 10, only eleven were denied, and, of these, six were at least in part non-substantive denials (the remaining nine petition responses either stated that they granted (two) or granted in part and denied in part (seven) the petitions). Failing to distinguish between denials on the merits and those based on non-substantive grounds significantly overstates the rate of true petition denials. Therefore, claims about innovators' use of citizen petitions that are based on statistics that intermingle substantive and non-substantive denials are flawed.

Moreover, it is incorrect to assume that even substantively denied petitions are automatically frivolous. Indeed, neither of the principal studies analyzing the approval rates of citizen petitions attempted to evaluate the merits of petitions that were denied.[29] As Commissioner Gottlieb has acknowledged, some section 505(q) petitions "raise difficult and important questions of public health that FDA should consider (even if the petitions are ultimately rejected)."[30] In fact, outside the context of section 505(q) petitions, FDA routinely issues interim responses recognizing that petitions "raise[] complex issues requiring extensive review and analysis by Agency officials" that prevent the agency from responding within the 180-day period prescribed by regulation.[31]

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[27] *See* Feldman 2017; Carrier 2016. One study purports to analyze only "substantive" decisions, claiming to exclude "petitions that were withdrawn or are pending, or where the FDA issued an interim response with no substantive decision." Carrier 2016, at 332 n.113. Based upon the number of "substantive" denials reported, however, that category appears to include what should be considered non-substantive denials of 505(q) petitions on procedural grounds. Indeed, the authors report that "[s]ince 2008, the FDA has reported that 68% of 505(q) petitions were denied, 5% granted, and 26% granted/denied in part. It is this 26% percent that we closely analyze . . . . ," *id*. at 332-333, n.113. This statement suggests that the authors accepted FDA's "denial" categorizations at face value and closely examined only "mixed decisions" to determine whether to classify them as grants or denials. As noted, the agency's denial data do not differentiate between substantive and non-substantive denials. *See supra* note 26 and accompanying text.

[28] For purposes of these calculations, "section 505(q) petition" means a citizen petition that included a certification pursuant to section 505(q)(1)(H) of the FDCA and was the subject of a response issued by FDA within 150 days of petition submission, reflecting that FDA's practice is to issue a response to a section 505(q) petition—whether a substantive or non-substantive response—by the statutory deadline. Where FDA views a petition as not subject to section 505(q), FDA often issues an interim response stating that the petition "raises complex issues requiring extensive review and analysis by Agency officials" that prevent the agency from responding within the 180-day period prescribed by regulation, thereby indicating that the 150-day deadline of section 505(q) does not apply to the petition. Petitions subject to such interim responses were deemed not to be section 505(q) petitions.

[29] *See* Carrier 2016, at 314-23; Feldman 2017, at 62 ("no attempt was made to judge the merits of the issues raised in the petition").

[30] Gottlieb Statement, at 9.

[31] *See, e.g.*, Letter from Carol J. Bennett, FDA, to Steven R. Peltier, Recordati Rare Diseases Inc., re: Docket No. FDA-2017-P-1077 (Aug. 15, 2017); 21 C.F.R. § 10.30(e)(2).

C. Assertions that innovator citizen petitions delay generic approval also are not supported by the facts.

Based on FDA's data, there is scant evidence that citizen petitions submitted by innovators delay approval of abbreviated applications. In eight years (FY 2008 through 2015), FDA received a total of 175 section 505(q) petitions.[32] Of those petitions, the agency resolved 167 by the end of FY 2015.[33] Forty-nine petitions (29%) were granted at least in part.[34] Only seven petitions (4%) resulted in a delay of approval of an abbreviated new drug application (ANDA),[35] and a total of ten applications[36] out of the 4,008 ANDAs and section 505(b)(2) applications approved during that time were delayed in approval due to a petition.[37] In other words, a citizen petition delay affected a tiny fraction—0.25%—of ANDAs and section 505(b)(2) applications during this period. That total includes two applications that were delayed by a petition submitted by an ANDA applicant, not an innovator, and one ANDA for which the delay in approval "had no impact on the marketing of the product because, as a result of a court's patent decision, the holder of the ANDA [was] enjoined from marketing the product for several years."[38] For the seven remaining applications that were delayed, the average delay was thirty-nine days.[39]

Moreover, FDA's simultaneous action on petitions and generic applications does not support an inference that the petitions delayed generic approval. An observer speculates that such simultaneous resolution suggests "that the FDA is delaying generic approval until it dispenses with the citizen petition."[40] There are alternative possible reasons for same-day denials, however. For example, FDA might have delayed issuing the petition response until it completed its ANDA review to ensure consistency between the decisions.[41] Indeed, FDA often considers petitions in parallel with the agency's review of the underlying ANDA[42] precisely because the agency's consideration of the application helps inform FDA's position on the issues raised by the petitioner. Moreover, taking simultaneous action on a petition and generic

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[32] Eighth Annual Report, at 5.

[33] *Id.* at 7.

[34] *Id.*

[35] *Id.* at 8.

[36] *Id.*

[37] Statement of Erika Lietzan, University of Missouri School of Law, before the U.S. House Committee on the Judiciary, Subcommittee on Regulatory Reform, Commercial, and Antitrust Law, at n.13 (July 27, 2017).

[38] *See* FDA, *Annual Report on Delays in Approvals for Applications Related to Citizen Petitions and Petitions for Stays of Agency Action for Fiscal Year 2008*, at 3 (Mar. 2009); FDA, *Fourth Annual Report on Delays in Approvals for Applications Related to Citizen Petitions and Petitions for Stay of Agency Action for Fiscal Year 2011*, at 3-4 (2012).

[39] *See supra* note 37, at n.13.

[40] *See* Carrier 2016, at 308; *see also* Feldman 2017, at 53.

[41] *See supra* note 37, at 4.

[42] *See id.* at 4-6*; see also, e.g.*, Fed. Defendants' Mem. in Supp. of Mot. to Dismiss and in Opp. to Pl's Mot. for Preliminary Injunction, *Teva Pharm. Indus. Ltd. v. Sebelius*, No. 14-CV-786, Docket No. 28, at 30-31 (D.D.C. May 12, 2014) ("FDA considers the citizen petition issues within the context of the petition docket, and reviews the ANDA in accordance with the distinct review process set forth in 21 U.S.C. § 355(j). In accordance with the statute, FDA has issued a response to Teva's petition, and the docket is now closed. FDA is continuing its review of any ANDAs.").

application reduces the likelihood of judicial review before the ANDA is approved.[43] Accordingly, same-day petition denials should not lead to the inference that the petitions delayed generic approval.

D. Current law provides FDA with ample authority to ensure that citizen petitions do not delay generic approval.

Those claiming that citizen petitions forestall generic approval overlook the agency's existing statutory authority to prevent any such delay from occurring. The statute prohibits FDA from delaying approval of an abbreviated application due to a petition unless FDA determines "that a delay is necessary to protect the public health."[44] FDA also has authority to summarily deny a petition that "was submitted with the primary purpose of delaying the approval of an application and . . . does not on its face raise valid scientific or regulatory issues."[45] We are aware of no instances where FDA has invoked this authority to summarily deny a petition (reinforcing that these petitions raise valid scientific and regulatory issues). FDA also may refer to the Federal Trade Commission (FTC) petitioning conduct that appears to raise concerns under antitrust law, and FDA has done so in certain cases. The risk of FTC enforcement action and/or a private antitrust suit serve as an effective check against improper use of the citizen petition procedure.

E. Claims regarding "serial petitions" ignore that, due to current FDA practice, an innovator might need to submit multiple filings to obtain a substantive response to its concerns.

Several speakers at the public meeting identified "serial" filings by innovators as a strategy to delay generic approval.[46] Under FDA's current practice, however, filing multiple petitions might be necessary to obtain a substantive response that could serve as the basis for meaningful judicial review. As noted, if an ANDA is not ready for agency action upon the 150-day deadline for a petition response, the agency typically denies the petition without comment on the merits. Moreover, it is the agency's practice not to further respond to the denied petition once it acts on the ANDA. Thus, if a petitioner receives such a non-substantive response and seeks to obtain a substantive ruling on the merits of the legal, regulatory, or scientific issues raised in the petition, the petitioner must submit a follow-up petition—likely one for which the 150-day deadline falls on or after the date of ANDA approval.

As PhRMA has noted previously, this FDA practice of issuing "non-denial denials" therefore creates perverse incentives that run counter to the purpose of section 505(q): (1) it

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[43] Answering a citizen petition before ANDA approval could subject FDA to a lawsuit before the generic product has entered the market because a citizen petition represents final agency action subject to judicial review, *see* 21 C.F.R. §10.45(d). By declining to respond to a citizen petition until the ANDA is approved, FDA makes it more difficult for the petitioner to prevail in litigation against the agency in two ways. First, the petitioner needs to seek a temporary restraining order and/or preliminary injunction to enable the court to resolve the dispute before launch, and, to obtain such relief, must make the demanding showing that it would suffer irreparable harm without judicial intervention. Second, if the petitioner fails to secure preliminary relief, the generic product will enter the market before the court rules on the merits, and courts historically have been reluctant to set aside ANDA approval and order a recall and removal of the generic drug from the market.

[44] FDCA § 505(q)(1)(A)(ii).

[45] *Id*. § 505(q)(1)(E).

[46] *See, e.g.*, David Balto, Coalition to Protect Patient Choice, Abuse of the FDA Regulatory Process and Possible Solutions, at 29, Docket No. FDA-2017-N-3615 (presentation at public meeting).

may dissuade petitioners from filing petitions early due to the likelihood that FDA will deny such petitions without a substantive response; and (2) it necessitates multiple petitions to ensure that a petition is under active review when FDA is ready to make an approval decision on a pending ANDA and thus, that the petitioner will receive a substantive response.[47] As PhRMA has noted previously, FDA should reconsider its practice of issuing non-substantive denials to provide stakeholders with more certainty.[48]

In any case, given the agency's practice of issuing non-substantive responses to section 505(q) petitions, it would be improper to infer that multiple petitions submitted to FDA on the same topic are intended to delay generic approval.

F. FDA should not presume that citizen petitions filed at particular times are intended to delay generic approval.

Contrary to one speaker's proposal, FDA should not "adopt a rebuttable presumption of delay for late-filed citizen petitions, [i.e.,] presume that brand-name manufacturer petitions pertaining to generic applications filed less than nine months before the expiry of the primary patent on the brand-name drug [are] a delaying tactic, which would require a preliminary finding that the petition would likely be granted based on compelling evidence in order to proceed to a full review."[49]

The premise underlying the proposed presumption—i.e., that petitions filed less than nine months before "primary" patent expiry are intended to delay generic entry—fails to account for the fact that the basis for a citizen petition may not become apparent until this timeframe.[50] For example, the innovator may learn about issues regarding the proposed generic product when it receives a paragraph IV notice with its accompanying "detailed statement of the factual basis of the opinion of the applicant that the patent is invalid or will not be infringed" during this time.[51] Before receiving that information, innovators often would not know there was a factual basis for a citizen petition. For example, only after reviewing a paragraph IV notice might the innovator learn that a generic applicant plans to use a formulation that differs from the RLD in ways that could affect safety and/or efficacy. Indeed, the proposed presumption is unnecessary because the existing certification requirement under section 505(q) is sufficient for FDA to assess whether a petition was submitted long after the basis for the petition became known to the petitioner.[52]

Finally, the proposal might not reduce the amount of agency resources that are devoted to the review of citizen petitions. A "preliminary finding that the petition likely would be granted" might be as resource-intensive as a full review, given the vagueness of the "compelling

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[47] PhRMA, Comments to Docket No. FDA–2011–N–0697, at 13 (April 2, 2012).

[48] *Id*. at 14.

[49] Transcript, The Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access, at 64 (July 18, 2017) (Innovation & Access Transcript) (statement by Ameet Sarpatwari, J.D., Ph.D., Harvard Medical School).

[50] Moreover, the speaker did not define "primary patent," so it is unclear how this proposal would function.

[51] FDCA § 505(j)(2)(B)(iv)(II).

[52] Each petitioner must certify, among other things, as to the approximate date when the information forming the basis for the petition became known to the petitioner, and supplemental information or comments to a petition must include a verification that, among other things, the submitter has not intentionally delayed submission. *See id*. § 505(q)(1)(H) & (I); 21 C.F.R. § 10.31(c) & (d).

evidence" standard. A less thorough review would create the risk that the agency might dismiss a petition that, on closer review, would be found to raise legitimate safety or efficacy concerns about proposed ANDA products. As Commissioner Gottlieb has recognized, "[i]t can be difficult in many cases to know prior to review which petitions" "raise difficult and important questions of public health that FDA should consider (even if the petitions are ultimately rejected)" and which do not.[53]

II. REMS

The Federal Register notice states that "[r]estrictions on distribution, either required by innovators or as part of a REMS ETASU [(elements to assure safe use)], can prevent generic companies from obtaining drug products for bioequivalence and other testing to support ANDA submissions."[54] The notice also states that "challenges in reaching . . . agreement" on the required single, shared system (SSS) "may cause delays to generic competition."[55] In addition, at the public meeting, topics raised included the issue of whether patents relating to REMS are eligible for listing in the Orange Book.

PhRMA believes that REMS do not upset the intended balance of Hatch-Waxman and that FDA has appropriate authority in this area. FDA has used its REMS authority to approve a number of important innovative drugs with serious safety risks that otherwise could not have been approved. Moreover, FDA has also approved (or tentatively approved) generic versions of many drug products subject to REMS with ETASU. Of the 44 REMS with ETASU programs, 10 are SSS—meaning that generic versions have been approved.[56] REMS with ETASU therefore do not preclude generic competition.

As explained below, PhRMA believes that FDA can take several additional actions within its current statutory authority to promote generic company access to drug samples and to implement the SSS provision of the FDCA to facilitate generic entry. For example, FDA should issue final guidance for generic applicants to obtain letters confirming their bioequivalence (BE) studies contain comparable safety protections to the innovator REMS, and that final guidance should resolve key issues left open in the draft guidance on this topic (the 2014 Draft Guidance).[57] Also, if FDA decides to publicly release those letters, the agency should follow its regulations regarding the protection of trade secret or confidential commercial information and present the letters in their proper context. The agency should clarify its statements concerning "[r]estrictions on distribution" and reject the proposal to allow foreign comparator products to serve as reference standards for BE testing. Finally, the agency should consider several factors in more broadly exercising the agency's authority to waive the SSS requirement and continue to recognize that REMS patents are eligible for listing in the Orange Book.

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[53] Gottlieb Statement, at 9.

[54] 82 Fed. Reg. at 28,495.

[55] *Id*.

[56] FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)* (as of Nov. 17, 2017), https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[57] *See* FDA, Draft Guidance for Industry, *How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD* (Dec. 2014) (2014 Draft Guidance).

A. Access to Samples

1. FDA can take meaningful steps using its existing statutory authority to address concerns about obtaining samples of drug product.

The Federal Register notice states that despite the agency's publication of the 2014 Draft Guidance, "generic companies have reported continuing difficulties in obtaining sufficient samples of drug products for testing." The agency asks, "What additional actions should FDA take, within its legal authority, to promote access to these drug products for generic companies seeking to conduct studies required to support ANDA submissions?"[58] FDA's 2014 Draft Guidance proposes a process for prospective ANDA applicants to obtain letters from the agency stating that BE study protocols contain safety protections comparable to a REMS with ETASU.[59] The 2014 Draft Guidance has not been finalized, however, and it leaves open the following important issues, which PhRMA identified in our February 2015 comments on the draft.[60] PhRMA recommends that FDA address these concerns in final guidance.

As an initial matter, PhRMA recommends that the final guidance acknowledge the important safety functions of REMS with ETASU. In particular, the final guidance should recognize that FDA's review of proposed study protocols must reflect the critical role of the ETASU in ensuring that the benefits of the drug outweigh its known serious risks, including to BE study participants. If FDA has imposed a REMS with ETASU, the agency must have found that, due to the drug's "inherent toxicity or potential harmfulness," the drug product could be approved "only if, or would be withdrawn unless," the ETASU were required "to mitigate a specific serious risk listed in the labeling of the drug."[61]

The final guidance also should acknowledge that REMS with ETASU for RLDs are designed through a deliberative process, and it should provide for a similarly robust review of BE study protocols to ensure safety. In particular, the final guidance should provide meaningful detail on how FDA plans to ensure that a BE study contains adequate safety measures to protect research participants. FDA issued a detailed, 34-page draft guidance document addressing the content of proposed REMS document for prescription medicines.[62] By contrast, the 2014 Draft Guidance does not provide detailed guidance on patient safety issues for BE testing of generic medicines subject to REMS with ETASU. For example, it does not describe: (1) how FDA will determine which elements (if not all the elements) of the RLD's labeling and ETASU are necessary to conduct the study safely; (2) the standards that FDA will use to determine whether the proposed study (including the protocols, informed consent forms, and informational materials) provides "comparable" safety protections to those in the ETASU; or (3) whether and how an implementation system for an ETASU relates to the prospective ANDA applicant's clinical studies. The final guidance should address these gaps to ensure that participants in BE testing receive the same level of safety protection as those who receive the drug outside a clinical trial. The final guidance also should provide specific examples as to how each ETASU should be implemented in a BE study and address the necessary content of informed consent forms and

[58] 82 Fed. Reg. at 28,495.

[59] 2014 Draft Guidance, at 3-4.

[60] *See* PhRMA, Comments to Docket No. FDA-2014-D-1891 (Feb. 3, 2015).

[61] FDCA § 505-1(f)(1).

[62] FDA, Draft Guidance for Industry, *Format and Content of a REMS Document* (Oct. 2017).

informational materials that will be distributed to the study investigators, pharmacists, and subjects.

PhRMA further recommends that the final guidance clarify the legal basis for, and the scope of, the agency's statement that it will not consider an innovator's provision of samples to a generic applicant in possession of a letter described in the 2014 Draft Guidance to violate the innovator's REMS.[63] The 2014 Draft Guidance does not identify the statutory basis for this approach, nor does it clarify whether it reflects an exercise of enforcement discretion or an interpretation of the FDCA. It does not define "sufficient" quantities of drug that the RLD sponsor may provide to the ANDA applicant consistent with the 2014 Draft Guidance, indicate whether an innovator must obtain the ANDA applicant's confirmation that the transferred drug product will be used only in accordance with the FDA-reviewed study protocol(s), or state whether innovators need to take any other steps to ensure that the sale will not be deemed to be a REMS violation. Nor does the 2014 Draft Guidance address whether an innovator may sell samples subject to a REMS with ETASU to an ANDA applicant without such a letter. It is essential that FDA clarify these points given that violations of the statutory REMS provisions carry the potential for significant penalties, including both criminal prosecution and civil monetary penalties.[64]

Finally, FDA should ensure routine involvement of CDER personnel with necessary expertise in developing and evaluating REMS with ETASU in BE study protocol review. The 2014 Draft Guidance states that personnel in CDER components outside the Office of Generic Drugs "may be consulted as necessary" in the review of subject protections in prospective ANDA applicants' draft protocols, informed consent forms, and informational materials.[65] PhRMA believes FDA instead should routinely involve individuals from the CDER components that have expertise and experience in developing and evaluating REMS with ETASU for RLDs: the Office of New Drugs, the Office of Surveillance and Epidemiology, and the REMS Oversight Committee.

A final guidance addressing these issues would give our members more confidence that, when they provide samples to generic developers, the samples will be handled and used safely, and our members will not be subject to liability.

2. Any public disclosure of REMS communications should comply with FDA's regulations and should present the letters in their proper context.

Commissioner Gottlieb has indicated that FDA is "considering whether to make [REMS] letters from FDA publicly available, to make more widely known the instances where generic drug makers may be having trouble getting access to branded drugs."[66] PhRMA understands "REMS letters" to refer to the letters FDA describes in its 2014 Draft Guidance that state that a generic applicant's BE study protocols contain safety protections comparable to a REMS with ETASU. PhRMA offers the following comments on this proposal.

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[63] *See* 2014 Draft Guidance, at 4.

[64] FDCA §§ 301, 303, 502(y), 505(p).

[65] 2014 Draft Guidance, at 3.

[66] Scott Gottlieb, M.D., Commissioner of Food and Drugs, Opening Remarks for Part 15 Public Meeting on Generic Drug Competition (July 18, 2017) (Gottlieb Opening Remarks).

If FDA proceeds with the public release of REMS letters, it must follow its regulations implementing the Freedom of Information Act (FOIA) in connection with any such public disclosure. In particular, FDA must redact from the letters any trade secret or confidential commercial information of either the prospective ANDA applicant or RLD sponsor.[67] Before releasing any information that reasonably could be considered trade secret or confidential commercial information, FDA must notify the submitter and consider any objections to disclosure, consistent with 21 C.F.R. § 20.61(e).

PhRMA is concerned, however, with the implication that the agency's REMS letters somehow evince that "generic drug makers may be having trouble getting access to branded drugs."[68] Such letters do not demonstrate an access problem but instead demonstrate that the generic applicant has obtained FDA's confirmation that it has instituted appropriate safety measures. FDA should take appropriate measures to present REMS letters in context and, to this end, should begin by clarifying that an innovator's request that a generic applicant obtain such a letter is entirely appropriate, consistent with the 2014 Draft Guidance, and in no way demonstrates an access issue.

PhRMA also recommends that FDA take further steps to provide necessary context and balance in connection with any release of REMS letters. For example, FDA should consider giving the innovator the opportunity to submit its response to the recipient of a REMS letter for publication on FDA's website alongside the REMS letter (subject to appropriate redactions of trade secret or confidential commercial information). Also in the interest of providing context, FDA should post information about the length of time taken by the agency in its review of prospective ANDA applicants' proposed study materials before issuing REMS letters, as well as the number of requests for these letters granted and denied. This information will help provide a more complete picture of the REMS letter process.

Finally, FDA should make public further information underlying the Commissioner's statement that FDA "has received more than 150 inquiries from generic companies that want to develop generic drugs but tell us they are unable to do so because they cannot get access to supplies of the RLD to do the testing needed for a generic application."[69] For example, the agency should clarify its definition of an "inquiry," the timeframe over which these 150 inquiries were received, how many preceded and succeeded FDA's issuance of the 2014 Draft Guidance, how many of these 150 inquires involved a prospective applicant who obtained a REMS letter in accordance with the 2014 Draft Guidance, how many related to products having REMS with ETASU, and what efforts a prospective applicant must have made to obtain supplies of the RLD before making a contact that FDA logged as an "inquiry."

3. PhRMA seeks clarification on FDA's statements concerning "restrictions on distribution."

FDA has requested input on actions that the agency can take "within its legal authority" regarding "[r]estrictions on distribution."[70] The meaning of "[r]estrictions on distribution," as used by FDA, warrants clarification; this term could conceivably include common legal

[67] 21 C.F.R. § 20.61(c).

[68] Gottlieb Opening Remarks.

[69] Gottlieb Statement, at 6.

[70] 82 Fed. Reg. at 28,495.

requirements affecting drug distribution, such as prescription and drug supply chain requirements. Moreover, if FDA determines that it lacks statutory authority in this area, the agency could refer concerns about allegedly anticompetitive practices with respect to samples of non-REMS drugs to the FTC, given the commercial and competition-related nature of these issues.

4. The proposal to allow ANDA applicants to use foreign-approved products as reference standards in BE studies would raise scientific, safety, and legal issues.

One speaker at the public meeting suggested that FDA permit ANDA applicants to use a foreign-approved innovator product, rather than the FDA-approved RLD, as a reference standard in BE studies if the applicant is unable to obtain samples of the RLD.[71] Under this proposal, the ANDA applicant would "provide evidence and confirmation that" the foreign comparator product is "the same product[]" as the RLD.[72] PhRMA believes this proposal raises legal, scientific, and safety concerns.

As a legal matter, section 505(j)(2)(A)(iv) requires that the ANDA include "information to show that the new drug is bioequivalent to the [RLD]," not to a foreign comparator serving as a proxy for the RLD. Although FDA's regulations authorize the agency to accept "any . . . approach deemed adequate by FDA to measure bioavailability or establish bioequivalence," FDA should not deem a demonstration of BE to a different product to be "adequate . . . to establish bioequivalence" of the proposed generic product.[73] Moreover, the information needed to establish that the foreign comparator and the RLD are the same is beyond the scope of what an applicant may submit in an ANDA. The FDCA makes clear that an ANDA may include only specified types of information, none of which is data to demonstrate the sameness of a foreign comparator and RLD.[74]

As a matter of science and safety, permitting substitution of a foreign comparator for the RLD in a BE study would undermine FDA's established practice of "select[ing] a single reference standard to ensure the greatest level of consistency between a generic drug and its RLD and among generic drugs."[75] Accepting BE studies conducted using a foreign comparator would call into question the therapeutic equivalence (and hence substitutability) of generic drug products for which BE was demonstrated using different comparator products. As FDA has recognized, "[t]he premise underlying the Hatch-Waxman Amendments is that . . . drug products" that are bioequivalent and meet the other ANDA approval requirements "are therapeutically equivalent and can be substituted for each other with the 'full expectation that the substituted product will

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[71] *See* Innovation & Access Transcript, at 228-29 (statement by Ms. Candis Edwards, Amneal Pharms.).

[72] *Id*. at 229.

[73] 21 C.F.R. § 320.24(b)(6).

[74] FDCA § 505(j)(2)(A). *Sanofi-Aventis U.S. LLC v. FDA* would not support FDA's acceptance in an ANDA of the type of data proposed here. There, the court held that required immunogenicity data were relevant to the proposed generic product's purity and therefore, were among the chemistry, manufacturing, and controls data that an ANDA must include. *Sanofi-Aventis U.S. LLC v. FDA*, 842 F. Supp. 2d 195, 209-10 (D.D.C. 2012). By contrast, however, this proposal would require the submission of data intended principally to demonstrate the properties of the foreign-approved comparator product (i.e., the sameness of that product and the RLD), not the proposed generic product—and therefore would fall outside the scope of what may be required in an ANDA. *See* FDCA § 505(j)(2)(A).

[75] FDA, Draft Guidance for Industry, *Referencing Approved Drug Products in ANDA Submissions* (Jan. 2017), at lines 231-235 (footnote omitted).

produce the same clinical effect and safety profile as the'" RLD.[76] Using a foreign comparator product as the reference standard would result in an inadequate showing of BE and thus, would call into question the safety and effectiveness of the generic product.

Finally, it is unclear how an ANDA applicant could demonstrate that the RLD and foreign comparator are the same—and, therefore, that the proposed generic drug and RLD are the same, as required for approval under section 505(j)(4)(C)—without access to the RLD, which the proposal assumes would be impossible. Therefore, an ANDA applicant is unlikely to be able to adequately establish sameness under the proposal.

B. PhRMA supports broader exercise of FDA's existing SSS waiver authority on a case-by-case, fact-specific basis.

The Federal Register notice also asks, "How should FDA apply its statutory authority to waive [the] requirement to implement a 'single, shared system,'" to avoid delays caused by "challenges in reaching such an agreement?"[77] PhRMA believes that FDA may more broadly exercise its existing waiver authority based on a determination that the burdens of an SSS outweigh its benefits,[78] taking into account a wide range of considerations, including the following factors:

- The length of time during which the parties have been negotiating toward an SSS without reaching agreement;
- The number of parties involved in the SSS negotiations; and
- The impact on health care providers, patients, the ANDA applicant, and the RLD sponsor.

FDA should consider these factors in determining whether SSS waivers are appropriate on a case-by-case, fact-specific basis. This approach is superior to setting a fixed time period within which SSS negotiations must be concluded, after which FDA will automatically grant a waiver if the parties have not reached agreement. Negotiations toward an SSS can involve a number of complex issues, and the time needed to complete them might vary across products and product classes, making a one-size-fits-all deadline for SSS negotiations inappropriate.

C. REMS-related patents are not, and should not be, excluded from listing in the Orange Book.

Two speakers at the public meeting took the position that REMS patents should be ineligible for listing in the Orange Book, arguing that "they do not claim 'the drug' or 'a method of using' the drug, but instead claim a method or system of mitigating a drug's risks."[79] Patents

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[76] Letter from Janet Woodcock, M.D., FDA, to J. Michael Nicholas, Ph.D., Teva Pharmaceuticals, re: Docket No. FDA-2015-P-1050, at 6 (quoting FDA, Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book), 35th ed., at viii).

[77] 82 Fed. Reg. at 28,495.

[78] FDCA § 505-1(i)(1)(B)(i).

[79] *See* Michael A. Carrier & Brenna Sooy, *Five Solutions to the REMS Patent Problem*, 97 B.U. L. Rev. 1661, at 1672 (2017); *see also* Ameet Sarpatwari, J.D., Ph.D., Harvard Medical School, Ensuring Timely Availability and Use of Low-Cost, High-Quality Generic Drugs, at 6 (presentation at public meeting) (Sarpatwari Presentation).

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. A REMS patent may be listed if it meets the criteria set forth in 21 C.F.R. § 314.53—i.e., if it claims an approved method of use as described by the approved labeling.[80]

III. Post-Approval Reformulations and Other Changes

FDA's Federal Register notice asks how post-approval changes to innovator drug products, such as new formulations, affect the Hatch-Waxman balance.[81] In addressing this topic, speakers at the public meeting suggested that FDA apply a higher approval standard for post-approval changes to drugs. PhRMA believes that post-approval innovations, including modifications to products and studies of new uses, play an important role in the Hatch-Waxman balance and should be incentivized. We further believe that FDA cannot and should not implement the proposal for a heightened approval standard for post-approval changes to approved drugs.

A. Post-approval changes are a critical part of pharmaceutical innovation and the Hatch-Waxman balance, producing important treatment benefits for patients and advancing the standard of care.

Research and development do not stop with initial FDA approval of a drug; in addition to important post-approval monitoring of approved medicines, it is important to incentivize the sponsor to continue to explore and examine potential new uses or variations of the medicine. Modifications to a drug's route of administration, delivery device, or dosage form, for example, can have a valuable impact on a drug's safety, effectiveness, tolerability, adherence, or convenience. Further, a drug's therapeutic usefulness often is not limited to the disease for which it is studied initially; ongoing research post-approval may support additional indications in other disease areas, including those with unmet medical needs.

For instance, new dosage forms such as extended-release formulations allow for less frequent dosing and may improve medication adherence. As an example, long-lasting injectable formulations to treat schizophrenia allow the medicine to remain within a therapeutic range for an extended period of time, helping patients better manage their disease symptoms by eliminating the need for daily oral medication. The long-acting formulation helps patients remain on their treatments, improving their quality of life and reducing the potential need for costly in-patient care.[82] Also, orally disintegrating tablets offer patients with swallowing difficulties an alternate option for taking their medication and other advantages, such as avoiding induction of nausea and vomiting symptoms in cancer patients.[83] Following the rapid trajectory of the science, researchers also look beyond a medicine's initial indication to explore additional disease areas and conditions where the medicine may be impactful. Encouraging

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[80] *See* 21 C.F.R. § 314.53(b) (authorizing the listing of method-of-use patents "that claim indications or other conditions of use for which approval is sought or has been granted in the NDA").

[81] 82 Fed. Reg. 28,495.

[82] *See, e.g.*, Prescribing Information (PI), Invega Sustenna® (paliperidone palmitate) extended-release injectable suspension, New Drug Application (NDA) 022264 (June 2017); FDA, News Release, *FDA Approves New Injectable Drug To Treat Schizophrenia* (Oct. 6, 2015), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465801.htm.

[83] *See, e.g.*, PI, Zofran® ODT (ondansetron) orally disintegrating tablets, NDA 020781 (Oct. 2017).

further study and seeking FDA approval for uses that otherwise would be off-label also accords with FDA's public policy goals.[84]

FDA should continue to encourage innovation through post-approval changes and should strengthen incentives for this innovation where possible, in keeping with the goal of Hatch-Waxman to promote continual medical advances while facilitating generic market entry. Nonclinical and clinical programs can be required to develop these medicines, and the development costs can be significant. Further, it can be difficult for manufacturers to predict the precise advantages of product modifications when development programs are initiated, as additional knowledge is gained through ongoing research over time. The properties of such modified products may become apparent only after major investments in research have been made. And it can be more difficult to offset costs of these post-approval innovations, because these drugs will compete with lower-cost generic versions of previously-approved drugs developed with abbreviated clinical testing. Nevertheless, it is clearly in the interest of the public health to encourage investment in the development of new products that can offer advantages for patient care.

Providing IP protection for post-approval innovation does not negatively affect access to generic versions of the original product and therefore, furthers the Hatch-Waxman balance. Specifically, once the period of protection on the original product has ended, and provided there are no safety concerns, generic copies of the original product may be approved for marketing. Healthcare providers and payors can then decide whether clinical benefits offered by the improved branded product are more important than the cost savings available through use of the less expensive generic versions of the original product.

Existing incentives for post-approval innovations should be maintained and, where possible, enhanced or expanded, because such innovations can be very valuable for patients, including those who are unable to tolerate or benefit from the initially approved drug product and those who experience greater benefits from subsequently developed versions. These innovations may include, for example, innovations to the dosing schedule, which have been shown to increase compliance and reduce hospitalizations.[85]

B. <u>FDA cannot and should not require post-approval changes to meet a different approval standard.</u>

One speaker at the public meeting suggested that FDA could "raise the standard [for approval] when you have a 'me-too drug.'"[86] Additionally, one question from the FDA panel asked whether the agency should approve only certain types of postmarketing changes, including those that improve convenience, efficacy, tolerability, or adherence.[87] PhRMA

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[84] *See* FDA, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, at 5 (Jan. 2017) (FDA Memorandum).

[85] *See, e.g.*, Sutton SS, Magagnoli J, Hardin JW. *Impact of Pill Burden on Adherence, Risk of Hospitalization, and Viral Suppression in Patients with HIV Infection and AIDS Receiving Antiretroviral Therapy*. Pharmacotherapy. 2016 Apr;36(4):385-401 (concluding that single-tablet regimen was "associated with higher adherence rates and a lower risk of hospitalization" as compared to multi-tablet regiments).

[86] Innovation & Access Transcript, at 56 (statement by Michael Carrier, Rutgers Law School).

[87] *Id.*, at 252-53 ("When you were talking about post-approval changes, you said about the ability to improve tolerability, adherence—I believe you had four specific examples that you used. So my question is should there be a requirement to demonstrate any or all four of those when the agency approves any postmarketing type changes to the innovator?") (statement by Kathleen Uhl, M.D., FDA).

believes that FDA should not discourage the availability of multiple treatment options in a given therapeutic class. Rather, prescribers and patients should have the ability to choose among drug products that may differ in efficacy and safety (for example, in tolerability), and patients should benefit from competition among multiple branded options. Moreover, PhRMA strongly believes that post-approval changes should not be subject to a heightened approval standard. This approach would conflict with the FDCA, prevent companies from making necessary manufacturing and similar changes, and discourage the development of improved drug products.

As a legal matter, there is no basis in the FDCA for FDA to apply a different approval standard for original NDAs for new active ingredients, on the one hand, and modifications to previously-approved active ingredients submitted via a supplemental NDA (sNDA) or new NDA, on the other. The statute has one approval standard for NDAs and sNDAs.[88] The statute also does not differentiate between approval standards for first-in-class and "me-too" products. Further, it would be arbitrary and capricious for FDA to reach a different decision on the approvability of the same drug product based solely upon order of approval. For example, if a manufacturer sought approval of two routes of administration of the same active ingredient, oral and intravenous (IV), it would be arbitrary and capricious to apply a different approval standard to the IV drug based solely on whether it was approved first or second.[89]

Moreover, denying approval of a subsequent application unless the proposed product reflects an "improvement" in effectiveness, tolerability, convenience, or adherence would bar approval of important changes that might not meet that standard. For example, post-approval modifications to increase manufacturing efficiency or accommodate changes in the supply chain (for example, a switch to a lower-cost supplier or replacement of a supplier going out of business) might not meet this definition of an "improvement." Preventing manufacturers from making these types of changes could lead to drug shortages.

A heightened standard for approval of post-approval changes also would discourage companies from investing in further research into existing compounds, as sponsors would not be able to predict with certainty that the research would yield data demonstrating a product "improvement" that could receive FDA approval under the higher standard. This disincentive to further develop approved drugs would be counter to the public health interest in increasing treatment options for patients, especially those with unmet medical needs. Moreover, this disincentive would run counter to the emphasis FDA has placed on studying the benefits and risks of unapproved uses of approved drugs and seeking supplemental approval for these new uses.[90]

Other proposed changes are beyond the scope of FDA's existing statutory authority. Participants in the public meeting advanced additional proposals regarding post-approval drug changes, but FDA lacks authority to implement them under the existing statute. For example,

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[88] *See* FDCA § 505(d).

[89] *See Indep. Petroleum Ass'n of America v. Babbitt*, 92 F.3d 1248, 1258 (D.C. Cir. 1996) ("An agency must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so."); *Ferring Pharms. Inc. v. Burwell*, No. 15-0802, 2016 WL 4734333, at *10 (D.D.C. Sept. 9, 2016) (holding that FDA's interpretation of the statutory provision governing new chemical entity exclusivity for fixed-dose combination products was arbitrary and capricious because "the exclusivity determination for the single-entity products might have changed depending upon the order in which the drug products were approved.").

[90] *See* FDA Memorandum, at 5.

FDA is not authorized to deny approval of reformulations or other product changes based upon a finding of subjective anticompetitive intent, because that is not among the grounds upon which FDA can deny approval.[91] This proposal also would be impracticable because it would require FDA to engage in a resource-intensive inquiry into the sponsor's intent and would lead to inconsistent results where the approvability of the same reformulation would depend upon the agency's findings as to the sponsor's subjective intent rather than the product itself.

C. The agency can take steps within its existing authority to preserve the Hatch-Waxman balance with respect to post-approval changes.

Consistent with its current authority under the FDCA, FDA could take actions to maintain the Hatch-Waxman balance in the context of post-approval modifications. First, FDA may refer cases of alleged anticompetitive conduct to the FTC, as it has done in the past. Second, FDA should make timely and transparent exclusivity decisions to provide certainty to both innovators and generic developers. At present, FDA sometimes declines to decide on a drug product's eligibility for marketing exclusivity at the time of approval. Rather, the agency defers a decision until some later date—as late as when an ANDA is ready for approval. This is true not only for innovator exclusivities, such as three-year exclusivity, but also for 180-day first applicant exclusivity for ANDAs.[92] More timely publication of exclusivity determinations would provide greater predictability and certainty for both innovators and generic drug developers and enable generic drug makers to develop and plan for the launch of generic versions of improved products as early as possible.

IV. Product Appearance

One speaker at the public meeting proposed that FDA require generic drug products to have the same appearance as the RLD.[93] A generic product can be therapeutically equivalent to an RLD despite differences in appearance,[94] and the speaker's suggestion overlooks the

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[91] FDCA § 505(d). One speaker suggested that patent information submitted for listing should be accompanied by "a competition statement, that says that competition will not be harmed by listing these patents in the Orange Book." Innovation & Access Transcript, at 336 (statement by David Balto, Coalition to Protect Patient Choice). This proposal asks FDA to implement a proposal that lacks any statutory basis. *See* FDCA § 505(j)(7)(A)(i). Indeed, such a statement is incongruous in the context of patents. The criteria for listing presupposes that the patent may be the subject of infringement. *See id*. § 505(b)(1) (requiring the listing 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.") Including a statement to the effect that competition will not be harmed by a patent implicates philosophical questions about patents themselves that fall outside of FDA's purview.

[92] *See, e.g.*, Memorandum from CDER Exclusivity Board to NDA 022272 Re: Three-Year Exclusivity Recommendation for Oxycontin (oxycodone hydrochloride) Controlled-Release Tablets (NDA 022272, S014) (Mar. 7, 2015) (exclusivity recommendation for sNDA approved on Apr. 16, 2013); FDA, Draft Guidance for Industry, *180-Day Exclusivity: Questions and Answers*, at 27 (Jan. 2017) ("In some circumstances, when a first applicant is ready for final approval, FDA may refrain from making a formal determination regarding that applicant's eligibility for 180-day exclusivity. Specifically, if FDA's review of the ANDAs for the drug product indicates that a formal determination of eligibility for 180-day exclusivity is not necessary (e.g., if there are no subsequent ANDAs or the subsequent ANDAs are likely more than 180 days away from final approval), FDA may refrain from making a formal determination regarding eligibility for 180-day exclusivity.").

[93] *See* Sarpatwari Presentation, at 8.

[94] FDA, Orange Book (37th ed. 2017), at xi ("Products evaluated as therapeutically equivalent . . . may differ in other characteristics such as shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration date/time, and, in some instances, labeling.").

important and beneficial purposes served by distinctive physical appearance, which include facilitating the safe use of approved drugs.[95] Distinctive elements of a drug product's physical appearance—such as a pill's color, size, shape, and code imprint—convey important information about the source of a specific product to pharmacists and patients. As a result, a pill's distinctive appearance, for example, can help pharmacists and patients avoid confusion about the source of a drug product that may contribute to medication errors. Further, a patient who experiences an adverse event might be more familiar with a drug product's physical attributes than with the drug product's other identifiers, such as the manufacturer's name or National Drug Code. As such, a drug product's distinct physical appearance could facilitate the accurate reporting of adverse drug experiences, which would help manufacturers and FDA to detect potential safety or quality issues, including potential bioinequivalence problems.

PhRMA is also concerned that the proposal does not appear to take into account that variation in product appearance may alert patients to changes in the source of their medication. The proposal seems premised on the concept that the innovator drug and all generic drug products referencing it should be identical in physical appearance (other than required code imprints) so that patients will not observe a difference if they receive products made by a different manufacturer. This premise is inconsistent with those state pharmacy practice laws requiring a patient to be notified if a switch occurs.[96] Indeed, if the generic drug for a particular formulation shared the same physical appearance, a patient might be misled about the source of her medication and believe that it continues to be made by the same manufacturer, even when the pharmacist has switched from one manufacturer to another. This situation would run counter to the intent of these state laws, as well as the long-held positions of many drug safety organizations.

A product's physical appearance also can, if sufficiently distinctive, qualify as trade dress that, like a traditional trademark, serves to distinguish between products from different manufacturers. Trade dress as a source identifier is protected under the Lanham Act,[97] and these IP rights should be taken into account in crafting regulatory policy. Finally, restrictions on distinctive physical appearances would raise First Amendment concerns because trade dress can be considered a protected form of non-verbal expression. Prohibiting variations in physical appearance would infringe upon manufacturers' First Amendment rights by limiting their ability to develop trade dress to serve as a source identifier of their respective products.[98]

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[95] FDA's guidance on the physical attributes of generic tablets and capsules offers recommendations based on scientific literature for determining a generic drug product's physical appearance, as compared to the RLD, to allow for a comparable patient experience in swallowing tablets and capsules. *See* FDA, Guidance for Industry, *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules* (June 2015). It does not require that a generic product be identical in physical appearance to the RLD. Moreover, FDA regulations require that solid oral dosage forms include "a code imprint that, in conjunction with the product's size, shape, and color, permits the unique identification" of the product and manufacturer or distributor. 21 C.F.R. § 206.10(a).

[96] *See, e.g.*, Tenn. Code Ann. § 53-10-210(b); Utah Code Ann. § 58-17b-605(2)(a).

[97] *See* 15 U.S.C. § 1051 et seq. For example, the Lanham Act provides a cause of action against "[a]ny person who . . . uses in commerce any word, term, name, symbol, or device, or any combination thereof . . . which is likely to cause confusion, or to cause mistake, or to deceive . . . as to the origin . . . of his or her goods, services, or commercial activities." *Id*. at § 1125(a).

[98] *See Gold Coast Publ'n, Inc. v. Corrigan*, 42 F.3d 1336, 1344 (11th Cir. 1994) (applying a First Amendment analysis to government restrictions on trade dress, specifically restrictions on the "color and size of lettering on newsracks"); *see also Hurley v. Irish-Am. Gay, Lesbian & Bisexual Grp. of Boston*, 515 U.S. 557, 569 (1995) ("[T]he Constitution looks beyond written or spoken words as mediums of expression."); *ETW Corp. v. Jireh Pub.*, Inc., 332 F.3d 915, 924 (6th Cir. 2003) ("The protection of the First Amendment is not limited to written or spoken words, but includes other

(continued…)

V. Issues Beyond the Scope of Hatch-Waxman

Several speakers at the public meeting and commenters to the public docket raised issues outside the scope of FDA's implementation of Hatch-Waxman. In particular, a number of commenters addressed issues relating to the BPCIA, the Patent Trial and Appeal Board's (PTAB) IPR process, and the government's use of march-in rights under the Bayh-Dole Act. With respect to the BPCIA, PhRMA strongly believes the statutory twelve-year exclusivity period for biologics appropriately reflects the substantial R&D investment required to bring a biologic to market. And, with respect to FDA's implementation of the BPCIA, PhRMA has submitted comments to the relevant dockets setting forth PhRMA's positions.[99] As to the PTAB's IPR process, PhRMA believes the process should be modified to ensure due process protections and fairness to patent owners, and has submitted comments addressing IPR issues to the relevant dockets at the Patent and Trademark Office,[100] and further believes that Hatch-Waxman should be the sole framework for resolving applicable patent disputes concerning generic drugs. Finally, with respect to Bayh-Dole, PhRMA believes that the current system best fosters a research ecosystem conducive to innovation.[101] PhRMA will continue to work with FDA and other agencies, when and where appropriate, to address these important policy issues.

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mediums of expression, including music, pictures, films, photographs, paintings, drawings, engravings, prints, and sculptures.").

[99] *See, e.g.*, PhRMA, Comments to Docket No. FDA-2017-D-0154 (May 19, 2017) (commenting on FDA's draft guidance entitled "Considerations in Demonstrating Interchangeability with a Reference Product"); PhRMA, Comments to Docket No. FDA-2016-D-0643 (Jul. 26, 2016) (commenting on FDA's draft guidance entitled "Labeling for Biosimilar Products"); PhRMA Comments to Docket No. FDA-2015-D-4750 (May 13, 2016) (commenting on FDA's Draft Guidance entitled "Implementation of the 'Deemed to be a License' Provision of the [BPCIA]"); PhRMA, Comments to Docket No. FDA-2013-D-1165 (Oct. 6, 2014) (commenting on FDA's draft guidance entitled "Reference Product Exclusivity for Biological Products Filed Under [PHSA] Section 351(a)"); PhRMA, Comments to Docket No. FDA-2014-D-0234 (Aug. 12, 2014) (commenting on FDA's draft guidance entitled "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"); PhRMA, Comments to Docket No. FDA-2011-D-0611 (Apr. 16, 2012) (commenting on FDA's draft guidance entitled "Biosimilars: [Q&As] Regarding Implementation of the [BPCIA]"); PhRMA, Comments to Docket No. FDA-2011-D-0605 (Apr. 16, 2012) (commenting on FDA's draft guidance entitled "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product");PhRMA, Comments to Docket No. FDA-2011-D-0602 (Apr. 16, 2012) (commenting on FDA's draft guidance entitled "Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product").

[100] *See, e.g.*, PhRMA, Comments to Docket No. PTO-P-2015-0053 (Nov. 18, 2015); PhRMA, Comments to Docket No. PTO-P-2014-0031 (October 16, 2014).

[101] On this point, PhRMA agrees with comments submitted by a group of university associations raising concerns that expansion of march-in rights under Bayh-Dole would "impede[] progress against some of [society's] costliest and most challenging diseases to the detriment of public health and safety." *See* Ass'n of Am. Medical Colleges *et al.*, Comments to Docket No. FDA-2017-N-3615, at 1 (Sept. 8, 2017).

VI. Conclusion

PhRMA appreciates FDA's consideration of these comments and the opportunity to speak at the public meeting. We look forward to a continued dialogue with the agency and other stakeholders on these issues.

Respectfully submitted,

/s/
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/s/
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