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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Comments of the Generic Pharmaceutical Association Regarding Docket No. FDA-2011-N-0830: Abbreviated New Drug Applications and 505(b)(2) Applications.

The Generic Pharmaceutical Association (GPhA) acknowledges the Food and Drug Administration's (FDA's) efforts in issuing proposed regulations to implement various provisions of Title XI of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Pub. L. No. 108-173, 117 Stat. 2066, 2448. See FDA, Proposed Rule, Abbreviated New Drug Applications and 505(b)(2) Applications, 80 Fed. Reg. 6802 (Feb. 6, 2015) (Docket No. FDA-2011-N-0830) [hereinafter Proposed Rule].

GPhA represents the manufacturers and distributors of finished generic pharmaceutical products, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic pharmaceutical industry. Our members manufacture more than 90% of all generic pharmaceuticals dispensed in the U.S., and their products are used in more than three billion prescriptions every year. Generics represent greater than 86% of all prescriptions dispensed in the U.S., but only 27% of expenditures on prescription drugs. GPhA is the sole association representing America's generic pharmaceutical sector in the U.S. While this response letter represents the views of the association on certain aspects of the Proposed Rule, there is a diversity of positions within our membership.

The Proposed Rule is the latest in a series of actions[1] by FDA to preserve the balance created with the September 24, 1984 enactment of the Drug Price Competition and Patent

[1] For example, FDA published a proposed rule in October 2002, 67 Fed. Reg. 65,448 (Oct. 24, 2002), and a final rule in June 2003, 68 Fed. Reg. 36,676 (June 18, 2003), addressing the types of patent information that the sponsor of a New Drug Application (NDA) may submit to FDA for listing in an appendix to the Agency's Approved Drug Products with Therapeutic Equivalence Evaluations (the Orange Book). Subsequent to the MMA's enactment, FDA requested public comment on what additional regulatory steps might be necessary in light of the statutory changes, and what issues the changes might

Term Restoration Act (Hatch-Waxman Amendments), Pub. L. No. 98-417, 98 Stat. 1585 (1984). Under the Hatch-Waxman Amendments, Congress hoped to achieve balance between, on the one hand, the public health and cost benefits from the availability of low-cost and high-quality generic drugs, and, on the other hand, the need to reward those manufacturers who bring brand-name drug products to market. Many of the provisions in the Proposed Rule would significantly further this goal by restoring balance that has been lost as loopholes or the lack of clarity in current regulations are exploited.

FDA characterizes the Proposed Rule as amendments "to facilitate compliance with and efficient enforcement of" the Federal Food, Drug, and Cosmetic Act (FDC Act), and as an effort "to clarify and update" existing regulations based on recent court decisions and on the Agency's "practical experience" implementing the Hatch-Waxman Amendments. Proposed Rule at 6803. While GPhA agrees with this general characterization, the Proposed Rule includes myriad changes – many highly technical in nature – to the current Hatch-Waxman regulatory framework and mechanics that are significant to generic drug manufacturers. Moreover, GPhA notes that while the Proposed Rule does not specifically implement provisions of the MMA related to 180-day exclusivity, many of the elements of the Proposed Rule are necessarily related to 180-day exclusivity – both to qualifying as a "first applicant" eligible for exclusivity, and to forfeiting eligibility for such exclusivity.[2] Comments on major provisions of the Proposed Rule follow.

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raise (and how they might be resolved). See 69 Fed. Reg. 9982 (Mar. 3, 2004). The rulemaking FDA proposed in October 2002 was undertaken after the Federal Trade Commission (FTC) issued a report in July 2002 raising concerns about the timely introduction of generic drugs into the U.S. marketplace and amidst allegations that companies were engaging in anti-competitive behavior. See FTC, Generic Drug Entry Prior to Patent Expiration: An FTC Study (July 2002). In particular, the FTC report focused on multiple 30-month litigation stays arising from Paragraph IV certifications to later-listed patents, and the ability of a first Abbreviated New Drug Application (ANDA) filer to "park" 180-day exclusivity. The MMA, which addressed both issues, superseded certain sections of the June 2003 final rule concerning application of the 30-month litigation stay of ANDA and 505(b)(2) application approval, and the superseded regulations were subsequently revoked by technical amendment. See 69 Fed. Reg. 11,309 (Mar. 10, 2004).

[2] MMA Title XI includes three subtitles: (1) Subtitle A—Access to Affordable Pharmaceuticals; (2) Subtitle B—Federal Trade Commission Review; and (3) Subtitle C—Importation of Prescription Drugs. The Proposed Rule concerns only Subtitle A (primarily Sections 1101 and 1103) and seeks to adopt language to codify those statutory provisions. MMA Section 1102 altered the conditions under which a period of 180-day marketing exclusivity is granted, and established the conditions under which a first applicant could forfeit eligibility for such exclusivity. GPhA is hopeful that FDA will, at a later date, publish proposed rules concerning those provisions. Until then, GPhA understands that FDA will continue to implement the MMA's 180-day exclusivity provisions directly from the statute, and will address novel issues through informal adjudications. See Proposed Rule at 6807.

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Definitions (Proposed 21 C.F.R. §§ 314.3 and 314.108)

GPhA applauds FDA's efforts to clarify and update various definitions crucial to the efficient enforcement of the Hatch-Waxman Amendments. Some of the definitions FDA proposes replace or significantly modify decades-old definitions that have been unclear (e.g., "listed drug" and "strength"), or that became outmoded by virtue of the passage of time (e.g., "postmark") and the Agency's (and industry's) greater use of and reliance on electronic media.

In particular, GPhA agrees with FDA's proposed definition of "commercial marketing," altering the scope of the exclusion for transfer of a drug product for reasons other than sale. See Proposed Rule at 6812. FDA's proposal would clarify that an ANDA holder's shipment of a drug product to a party named in the ANDA for purposes described in the application does not constitute "commercial marketing" of the drug, thereby clarifying that such shipment does not trigger 180-day marketing exclusivity. GPhA recommends that FDA further clarify the definition of "commercial marketing" to specifically exclude charitable donations of drug product.

FDA's proposed definition of "Paragraph IV acknowledgment letter" to mean a written, postmarked communication from the Agency to an ANDA applicant stating that FDA has determined that an application containing a Paragraph IV certification is sufficiently complete to permit a substantive review should better facilitate implementation of the MMA's timing requirement for sending notice of a Paragraph IV certification to the NDA holder and to each patent owner. See id. at 6814; FDC Act § 505(j)(2)(B)(ii)(I). Moreover, FDA's inclusion of the term in proposed 21 C.F.R. § 314.101(b)(2) adequately addresses GPhA's prior request that FDA, in light of the MMA's revised notice requirement, amend 21 C.F.R. § 314.101(b)(2) to state that the Agency will notify an applicant "in writing via a postmarked notice" that an ANDA has been received. See GPhA Comment, Docket No. FDA-2004-N-0062-0012, at 4-5 (May 5, 2004).

FDA's complementary proposed definition of "postmark," Proposed Rule at 6815, which is adapted from an Internal Revenue Service regulation defining "electronic postmark," to accommodate electronic submissions should also facilitate Paragraph IV notice. In many cases, ANDA applicants have received filing communications from FDA both by electronic mail and by the U.S. Postal Service, causing confusion as to the date from which the statutory 20-day period should be calculated and the date by which notice must be sent.

In defining the term "substantially complete application," FDA notes that in order for an ANDA to be substantially complete, "any information referenced in the application must

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have been provided to the Agency," and uses as an example a situation in which an electronic submission is made that is not readable or that does not follow FDA's recommendations for electronic application format. Id. at 6816-17. While GPhA agrees that some applicant's errors in compiling an electronic submission may serve as grounds for refusing to receive an ANDA as not substantially complete, applicants should not be penalized when FDA is unable to read an electronic submission because of technical errors. Communication with an applicant will, in most cases, quickly clarify or remedy the error. In addition, ANDA applicants should also not be held accountable for FDA's inability to support standards or requirements due to technical challenges faced by the Agency. FDA has, in recent months, routinely refused to receive ANDAs because of technical challenges with hyperlinks and bookmarks in the eCTD format. In that respect, FDA should consider industry comments on recent guidance documents concerning refuse-to-receive standards (see, e.g., Docket Nos. FDA-2014-D-1292 and FDA-2013-D-1120) and provide clarity on the process for challenging refuse-to-receive decisions.

Submission of Orange Book Patent Information (Proposed 21 C.F.R. § 314.53)

FDA proposes several changes to the Agency's current regulations governing Orange Book patent listings that are both general and specific in nature. While some of the changes in the Proposed Rule "are intended to clarify the basis for requiring certain information, revise and streamline [the Agency's] requirements, and describe acceptable approaches to compliance with applicable regulations," Proposed Rule at 6818, other proposed changes are more substantive, including a proposal to enhance the current regulatory mechanism for challenging the accuracy or relevance of information listed in the Orange Book for method-of-use patents.

With respect to drug substance patents that claim only a polymorph of the active ingredient, FDA's regulations currently require submission of information on whether the patent claims a polymorph that is the same active ingredient as that described in the NDA. See 21 C.F.R. § 314.53(c)(2)(i)(M)(2), (ii)(N)(2). FDA proposes to revise these regulations to state that an NDA applicant is only required to provide information on whether a patent claims a polymorph that is the same active ingredient described in the pending application if the only basis on which the patent is eligible for listing is that it claims the polymorph. See Proposed Rule at 6820. GPhA supports FDA's proposed changes.

Method-of-use patents have been particularly nettlesome to ANDA applicants, largely because of the patent use codes and narratives by which such patents are listed in the Orange Book. Overbroad patent use codes have stymied generic competition. See Caraco Pharm. Labs. v. Novo Nordisk A/S, 566 U.S. __, 132 S. Ct. 1670, 1684 (2012)

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("An overbroad use code . . . throws a wrench into the FDA's ability to approve generic drugs as the statute contemplates."). The Proposed Rule includes myriad proposed changes to address these issues.

First, a proposed revision to 21 C.F.R. § 314.53(b)(1) replacing the word "claim" with "claim(s)" in the phrase "shall separately identify each pending or approved method of use and related patent claim" is intended to clarify that an NDA sponsor may list together on Forms FDA 3542a and 3542 multiple patent claims for a pending or approved method-of-use, respectively, but each approved method-of-use must be separately identified in the applicable form. Separate form listings will result in separate Orange Book patent use code entries and should greatly enhance the ability of generic applicants to appropriately and accurately address applicable patents. See Proposed Rule at 6820.

Second, FDA proposes to revise 21 C.F.R. § 314.53(b)(1), (c)(2)(i)(O)(2), (c)(2)(ii)(P)(2), and (c)(2)(ii)(P)(3) to "enhance compliance by NDA applicants with the requirements for identifying the specific section(s) of product labeling that correspond to the method of use claimed by the patent and, upon approval, describing the approved method of use claimed by the patent." Id. To achieve this enhanced compliance, an NDA sponsor would be required to "identify only the specific sections of product labeling that correspond to the specific portion(s) of the indication or other condition of use claimed by the patent" if the scope of the patent does not cover all uses of a drug product. Id. When the scope of the use claimed by a patent is narrower than the indication or other condition of use described in product labeling, the NDA sponsor "must identify only the specific sections of product labeling that correspond to the portion(s) of the indication or other condition of use claimed by the patent and not the broader indication or other condition of use in the product labeling which may include, but not be limited to, the use claimed by the patent." Id. These changes would facilitate FDA's consideration of labeling carve-outs, as well as generic applicants' patent assessment.

Third, FDA proposes 21 C.F.R. § 314.53(c)(2)(ii)(P)(3) to codify the Agency's longstanding requirement that the use code narrative supplied by an NDA sponsor on Form FDA 3542 contain sufficient information for the Agency and generic drug applicants to determine whether or not a labeling carve-out is possible. See id. ("If the scope of the method-of-use claim(s) of the patent does not cover every approved use of the drug, the NDA holder's 'use code' must contain only the specific portion(s) of the indication or other method of use claimed by the patent."). GPhA supports this proposal.

Later in the Proposed Rule, in the context of untimely filed patent information, FDA addresses when amendments to patent use code narratives will be considered late-listed.

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Specifically, in revisions to 21 C.F.R. §§ 314.50(i)(4) and 314.94(a)(12)(vi), FDA proposed that a use code revision will be considered untimely if "[t]he amendment is submitted more than 30 days after patent issuance and it is not related to a corresponding change in approved product labeling," or "the amendment is submitted more than 30 days after a corresponding change in approved product labeling." Id. at 6824. As such, an ANDA applicant would not be required to certify with respect to the untimely change. Like other related proposals, this revision is intended to "enhance NDA holders' compliance" with the requirement to accurately identify protected information. Id. GPhA supports this proposal.

FDA proposes to treat an original patent and a reissue of that patent as a "'single bundle' of patent rights." Id. at 6821. In a recent decision from the U.S. Court of Appeals for the Fourth Circuit, the Court set aside FDA's single bundle of patent rights interpretation of the law. See Mylan Pharms., Inc. v. FDA, No. 14-1522 (4th Cir. Dec. 16, 2014). The Court found, in a case concerning the pre-MMA version of the FDC Act, that FDA's interpretation was contrary to the statutory text, and that a reissue patent is a separate and distinct patent that can yield a separate period of 180-day exclusivity.

The Proposed Rule, which was clearly written well before the Fourth Circuit's decision, proposes to add 21 C.F.R. § 314.53(c)(2)(i)(J) and (c)(2)(ii)(K) to require an NDA sponsor to identify whether or not a patent is a reissue of a patent previously submitted for listing. FDA also proposes that a reissue patent listed in the Orange Book would adopt certain characteristics of its parent original patent. For example, if the original patent was late-listed (i.e., information on the patent was submitted to FDA more than 30 days after issuance or a relevant approval making the patent listable), the reissue patent is also considered late-listed. As such, a company with a pending ANDA would not be required to certify to the patent. See Proposed Rule at 6821. GPhA urges FDA to assess whether or not the Agency's proposal on reissue patents is valid in light of the Fourth Circuit's decision in Mylan.

FDA proposes to significantly alter the historically toothless patent information challenge and correction procedures at 21 C.F.R. § 314.53(f) with an enhanced mechanism that shifts Agency deference from NDA sponsors to ANDA applicants. That regulation currently provides that if a person disputes the accuracy or relevance of patent information listed in the Orange Book, FDA will ask the NDA sponsor to confirm the correctness of the patent information. Unless the sponsor acts on that request by withdrawing or amending the patent information, FDA will not otherwise alter the patent information, and will consider an ANDA in the context of what the NDA sponsor has submitted to FDA for Orange Book listing.

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Proposed § 314.53(f)(1) would first establish a 30-day deadline for an NDA sponsor to respond to a request from FDA conveying a challenge to the accuracy or relevance of patent information. Second, with respect to method-of-use patent disputes, and where no change is made by the NDA sponsor to the patent use code narrative, FDA is proposing to give deference to an ANDA applicant's interpretation of the scope of the patent. See id. at 6827-28.

GPhA supports FDA's proposed process regarding the correction of patent information for method-of-use patents and agrees with FDA that, if implemented, the proposed process would "cause NDA holders to be more circumspect in their original submission of patent information to FDA." Id. at 6828. The text of proposed § 314.53(f), however, does not appear to align specifically with the process described in the preamble to the Proposed Rule, and should be revised to more closely match the preamble discussion. In addition, GPhA proposes that FDA amend the 30-day deadline for an NDA sponsor to respond to a request from FDA conveying a challenge to the accuracy or relevance of patent information to 15 days. Fifteen days is the current and longstanding regulatory deadline when FDA notifies an NDA sponsor that a patent declaration form is incomplete or otherwise inadequate. See 21 C.F.R. § 314.53(c)(2)(ii).

Notice of Paragraph IV Certification (Proposed 21 C.F.R. § 314.95)

The MMA made certain changes to the FDC Act concerning the timing of when notice of a Paragraph IV certification must be provided. Specifically, the statute states that notice must be provided "not later than 20 days after the date of the postmark on the notice with which [FDA] informs the applicant that the application has been filed" if a Paragraph IV certification is in an original application, and "at the time at which the applicant submits the amendment or supplement" if the Paragraph IV certification is in an amendment or supplement to the application. FDC Act § 505(j)(2)(B)(ii).

FDA's Proposed Rule would implement the MMA's changes concerning notice timing, as well as make several other changes to more efficiently enforce the statute and to address certain strategies some applicants have adopted in an effort to either become a first applicant eligible for a period of 180-day exclusivity, or to jump-start the patent litigation process.

FDA proposes to revise its regulation at 21 C.F.R. § 314.95(b) to delineate the two timeframe limitations within which notice of a Paragraph IV certification to a listed patent can be provided to the NDA holder and patent owner(s): (1) the date before which notice may not be given; and (2) the date by which notice must be given. See id. at 6831.

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Proposed 21 C.F.R. § 314.95(b)(1) would reflect FDA's longstanding and general practice that Paragraph IV notice is improperly sent unless and until the Agency has notified an ANDA applicant that its application has been received in a "Paragraph IV acknowledgment letter." See id. To address the issue of so-called "premature notice," FDA proposes 21 C.F.R. § 314.95(b)(2) to provide that any notice sent before the receipt of a "Paragraph IV acknowledgment letter" is premature and invalid, and will not be considered to comply with the statutory notice requirement. See id. at 6832. FDA also proposes to amend 21 C.F.R. § 314.95(c)(3) to require that an ANDA applicant include in its notice letter a statement that the applicant has received a "Paragraph IV acknowledgment letter." See id. GPhA supports FDA's proposed approach.

With respect to an original application, FDA proposes to revise 21 C.F.R. § 314.95(b)(1) to require that an applicant send Paragraph IV notice on or after the date on which it receives a "Paragraph IV acknowledgment letter," but not later than 20 days after the date of the postmark on such acknowledgment letter. See id. With respect to an amended (once received) or supplemented (once approved) application, FDA proposes to revise 21 C.F.R. § 314.95(d) and to clarify the Agency's current regulations to require that an applicant send Paragraph IV notice to the NDA holder and patent owner(s) simultaneous with the submission of the amendment or supplement to FDA. See id. at 6834.

Under current law, if an ANDA applicant does not provide notice of a Paragraph IV certification simultaneous with an amendment or supplement, then FDA will consider the certification to be effective only as of the date that the applicant has perfected the certification with notice. See Purepac Pharm. Co. v. Thompson, 354 F.3d 877 (D.C. Cir. 2004). This could result in an applicant not qualifying as a first applicant eligible for 180-day exclusivity. FDA proposes an analogous consequence for sponsors of original applications, such that if an applicant fails to provide notice of a Paragraph IV certification within the 20-day statutory timeframe, the certification would not be considered perfected until such notice is sent, and FDA would "[move] forward the date of submission of the ANDA by the number of days beyond the required time frame that the applicant delayed in sending its notice," potentially resulting in an applicant not qualifying as a first applicant eligible for 180-day exclusivity. Proposed Rule at 6840. GPhA agrees with this FDA proposal. It creates a congruency with current law.

In an effort to eliminate so-called "serial" Paragraph IV patent certifications submitted by ANDA applicants hoping to qualify as a first applicant eligible for 180-day exclusivity, FDA also proposes to create a date certain by which Paragraph IV patent certifications may be submitted to the Agency. Specifically, FDA proposes that "any notice of paragraph IV certification is invalid if it is sent before the first working day after the day

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the patent is listed in the Orange Book." Id. at 6835-36. While GPhA understands that serial certifications place some administrative burden on FDA, GPhA is concerned that FDA's proposal would dilute the value of 180-day exclusivity by creating a situation akin to an "NCE-1 date" where multiple applicants qualify as first applicants eligible for 180-day exclusivity.

Patent Certification Requirements for Amendments and Supplements to ANDAs (Proposed 21 C.F.R. §§ 314.96 and 314.97)

FDA proposes to "clarify and augment the patent certification requirements" for ANDA amendments and supplements described in 21 C.F.R. § 314.94(a)(12)(viii)(C). Id. at 6847. Specifically, FDA would require an ANDA applicant to submit a patent certification (or recertification) if approval is sought for any of the following changes: "(1) [t]o add a new indication or other condition of use; (2) to add a new strength; (3) to make other than minor changes in product formulation; or (4) to change the physical form or crystalline structure of the active ingredient." Id. All four categories apply to ANDA amendments, while only the first two categories of changes apply to ANDA supplements. See id. at 6848.

With respect to "other than minor changes in product formulation," FDA proposes that "[a] new patent certification would not be required if the new formulation in the amendment is qualitatively (Q1) the same as the previous formulation (i.e., contains all of the same inactive ingredients) and quantitatively (Q2) essentially the same (i.e., each inactive ingredient differs by no more than plus or minus 5 percent from the previous formulation)." Id. at 6849. Non-Q1/Q2 changes would be considered major and require a patent recertification. GPhA believes that a determination of recertification should not be dependent on whether a major change has been made, but rather on the modified formulation in relation to the patent. This determination is best made by the ANDA applicant and not by FDA.

With respect to FDA's proposal to require a patent certification (or recertification) for amendments or supplements to add a new indication or other condition of use, FDA should clarify that such certifications do not need to be made to all Orange Book-listed patents, but only to patents to which a certification was not previously made and that covers the new use or condition.

Petition to Request a Change From a Listed Drug (Proposed 21 C.F.R. § 314.93)

FDA proposes to amend the Agency's regulation at 21 C.F.R. § 314.93 governing ANDA suitability petitions to codify the Agency's policy that if the drug product described in the

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petition is approved under an NDA, then neither the petition nor the listed drug identified in the suitability petition can serve as a basis for ANDA submission, and any pending ANDA submitted on the basis of the petition would not be eligible for approval. See id. at 6856-57.

GPhA agrees with FDA's proposal, but also takes this opportunity to urge the Agency to meet the statutory deadline to "approve or disapprove a petition . . . within ninety days of the date the petition is submitted." FDC Act § 505(j)(2)(C). FDA rarely meets this deadline, and the Agency's failure to act promptly serves as a disincentive to use the suitability petition process. See Kurt R. Karst, Letting the Devil Ride: Thirty Years of ANDA Suitability Petitions Under the Hatch-Waxman Act, 40 Wm. Mitchell L. Rev. 1260 (2014). The unattractiveness of the suitability petition process is exacerbated by the concern that during the long pendency of a petition, FDA may approve an NDA for the petitioned change, rendering the suitability petition moot.

Date of Approval of a ANDA (Proposed 21 C.F.R. § 314.107)

The 2003 MMA amended the statute to specify that a first applicant's eligibility for 180-day exclusivity is triggered and begins on the "date of the first commercial marketing of the drug (including the commercial marketing of the listed drug) by any first applicant." FDC Act § 505(j)(5)(B)(iv)(I). FDA proposes, as a replacement to its current regulation at 21 C.F.R. § 314.107(c)(3), describing the potential loss of 180-day exclusivity because of a first applicant's failure to actively pursue ANDA approval, a new regulation – proposed 21 C.F.R. § 314.107(c)(2) – to require a first applicant to submit correspondence to its ANDA notifying FDA within 30 days of the date of first commercial marketing of the drug product. See Proposed Rule at 6866. If a first applicant fails to notify FDA within the 30-day timeframe, then FDA proposes to deem the date of first commercial marketing to be the date of ANDA approval. See id.

FDA's proposal is inconsistent with the Agency's proposed definition of "commercial marketing." That definition requires that the approved drug actually be introduced or delivered for introduction into interstate commerce, outside the control of the applicant. See id. at 6876 (proposed 21 C.F.R. § 314.3(b)). FDA's proposal to deem a date of first commercial marketing without actual marketing cannot be squared with the statute, FDA's proposed and longstanding definitions of "commercial marketing," or with FDA's predecessor regulation at 21 C.F.R. § 314.107(c)(3), which the Agency has never enforced.

Refuse to Receive Process Proposed 21 C.F.R. § 314.101)

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GPhA would urge FDA to modify/clarify the "Refuse to Receive" ("RTR") process. In this regard, our members have of late expressed serious concerns. Specifically, FDA has been (1) transforming substantive, scientific issues into threshold filing issues; (2) issuing RTR letters based solely on minor, technical errors in electronic submissions; and (3) failing to provide adequate due process to applicants whose ANDAs were not accepted for filing.

As GPhA members noted in response to Docket No. FDA-2014-D-1292 and in meetings with the Agency, FDA has increasingly been transforming substantive, scientific issues into threshold filing issues. This practice, which has the effect of preventing these scientific issues from being reviewed by the very Agency experts who have the experience and responsibility for reviewing such matters, is inconsistent with the Agency's current regulations, which provide that "Receipt of an abbreviated new drug application means that FDA has made a threshold determination that the abbreviated application is sufficiently complete to permit a substantive review." 21 CFR § 314.101(b)(1). The Proposed Rule, however, would amend section 314.101(b)(1) by replacing the current criterion of "sufficiently complete to permit a substantive review" with the term "substantially complete application." While FDA states that this revision is not intended to alter the meaning of section 314.101(b)(1), in light of FDA's recent attempts to transform substantive, scientific issues into threshold filing issues, our members are worried that the proposed change will be used by the Agency to justify this worrisome trend. While we recognize that FDA is adding a definition of "substantially complete application" in section 314.3(b), we would urge FDA to add language to the preamble of the final rule to make clear that FDA's refusal to receive an ANDA must be based solely on a facial assessment of the application's completeness rather than a review or evaluation of the ANDA's substantive content or scientific merits.

GPhA members are also concerned with FDA's recent issuance of several RTR letters based solely on minor, technical errors in electronic submissions. In discussing "substantially complete applications," the Proposed Rule states that electronic submissions that are not readable or do not follow FDA's recommendations for electronic applications may not be considered substantially complete. Although we doubt that FDA can, as a matter of law, refuse to accept an application for receipt based on an applicant's failure to comply with nonbinding recommendations, we agree that that an applicant's errors in compiling an electronic submission may in some cases serve as grounds for refusing to receive an application. Applicants should not, however, be penalized when FDA is unable to read an electronic submission due to technical errors. Communication with an applicant will in most cases quickly clarify or remedy the error. Industry should also not be held accountable for the Agency's inability to support standards and or requirements due to technical challenges faced by the Agency. For example, the FDA

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should not be issuing RTR letters based on minor issues with hyperlinks and book marking in the eCTD format.

GPhA members are further concerned with FDA's failure to provide adequate due process to applicants whose ANDAs were not accepted for filing. FDA should consider the comments that industry submitted to the refusal to receive guidance dockets (Docket FDA-2014-D-1292, FDA-2013-D-1120) and provide an actual mechanism for ANDA applicants to challenge RTR letters. It is not lost on GPhA members that although section 314.101(a) allows for NDA applicants both to request an informal conference with FDA to discuss the basis for a refusal to file decision and to file the NDA under protest, there is no comparable provision in section 314.101(b) for ANDA applicants. FDA should take this rulemaking as an opportunity to correct this disparity. This is of particular importance to our members in light of the practices noted above, i.e., the increasing issuance of RTR letters based on (1) substantive, scientific issues that have been converted into threshold filing issues; and (2) minor, technical errors in electronic submissions, such as issues with hyperlinks and book marking in the eCTD format.

As noted above, FDA states in the Proposed Rule that it may issue RTR letters based on an applicant's failure to follow FDA's recommendations for electronic applications, which are set forth in FDA guidance documents. The Agency needs to clarify this statement as it is well established that recommendations in FDA guidance documents are nonbinding and, as a result, FDA may not refuse to accept an application for receipt based solely on an applicant's decision to utilize alternate approaches and that do not conform with nonbinding recommendations. Similarly, in proposed section 314.105(c) the Agency states that it is frequently called upon to determine, in its scientific judgment, the kind and quantity of data that is "required" to be in applications for particular types and classes of drugs to meet the statutory approval standards. In the very next sentence the FDA states that it makes available its views on particular types and classes of drugs "through guidance documents, recommendations, and other statements of policy." The clear implication, of course, is that the kind and quantity of data that is "required" to be in applications for particular types and classes of drugs can be found in guidance documents, recommendations, and other statements of policy. As noted above, this is simply not the case as FDA cannot establish "requirements" in such non-binding documents. The last sentence of section 314.105(c) needs to be either deleted or significantly revised so as not to misleadingly suggest that documents containing nonbinding FDA recommendations can ever contain filing "requirements."

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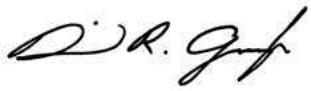
Should you have any questions regarding these comments, please do not hesitate to contact me. GPhA appreciates the opportunity to comment on the important issues raised in the Proposed Rule.

Sincerely,



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