Generic Pharmaceutical Association

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Comments on the Proposed Rule "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 78 Fed. Reg. 67985 (Nov. 13, 2013) [Docket No. FDA-2013-N-0500]

The Generic Pharmaceutical Association ("GPhA") is a voluntary, non-profit association comprised of more than 65 manufacturers and distributors involved in the generic pharmaceutical industry. GPhA's members provide consumers world-wide with generic medications that are as safe and effective as their brand-name counterparts, but at a fraction of the cost. Generic drugs approved by the Food and Drug Administration ("FDA") have the same high quality, strength, purity and stability as brand-name drugs. GPhA's members are dedicated to providing safe, high quality, generic pharmaceutical products to the American public and believe first, and foremost, in protecting patient safety and ensuring access to affordable medicines.

GPhA submits these comments on FDA's proposed rule, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products" (the "proposed rule"), issued on November 13, 2013.

FDA issued the proposed rule ostensibly to "create parity among application holders with respect to [] safety-related labeling changes by permitting [abbreviated new drug application ("ANDA")] holders to distribute revised generic drug labeling that differs in certain respects, on a temporary basis, from the [reference listed drug ("RLD")] labeling upon submission to FDA of a [changes being effected ("CBE-0")] supplement." (Proposed rule, 78 Fed. Reg. 67985.) The proposed rule raises serious concerns and, contrary to the stated purpose, would not promote the dissemination of important information to health care professionals or the general public regarding safety, risks, and use of prescription pharmaceutical products. Moreover, the proposed rule rests on a false premise: That the "generic drug industry" is a single coherent entity, rather than a collection of hundreds of small competitors.

Most concerning, FDA's proposed rule would create substantial confusion for pharmacists, doctors, nurses, patients, and others in the health care system by allowing multiple, different drug labels in the market for the very same product, upending 30 years of law and regulation. That would not only jeopardize patient safety, but also as a recent economic study has shown, would create billions of dollars in annual increased costs for consumers, taxpayers, large and small

businesses, and state and federal governments. The rule would decrease patient access, impede healthcare decisions and delivery, and make fewer generic drugs available.

GPhA and its members believe FDA's proposed changes to existing regulations:

(1) Exceed FDA's authority and are contrary to the express provisions of the Food, Drug, and Cosmetic Act ("FDCA");
(2) Would lead to unwarranted confusion for health care providers and consumers, and as a result, put patient safety at risk;
(3) Are not supported by any empirical evidence that ANDA applicants have not complied with their regulatory obligations historically or that the "incentives" for them to comply with those obligations have been altered in light of recent United States Supreme Court decisions;
(4) Are based on a flawed premise that ANDA applicants routinely receive or possess data that may constitute "newly acquired information" alerting them to a need to propose safety-related changes to product labeling;
(5) Threaten to undermine the confidence consumers and health care providers have in generic drugs because they are "the same" as their brand-name counterparts;
(6) Open the generic drug industry to massive and unwarranted state-law tort litigation and possible liability; and
(7) Would greatly increase the burdens on the generic drug industry and, therefore, would necessarily increase the costs of generic pharmaceutical products without an incremental benefit to patients.

Moreover, FDA has not provided any objective evidence of a need to change existing regulations.

1. The FDCA and Congress's Grant of Authority to FDA Does Not Permit FDA to Implement the Proposed Changes

a. The FDCA's Requirements and FDA's Authority

Under the FDCA, a drug may not be introduced or delivered for introduction into interstate commerce "unless an approval of an application filed pursuant to [21 U.S.C. §355(b) or (j)] is effective with respect to such drug." 21 U.S.C. §355(a). Congress vested "authority to promulgate regulations for the efficient enforcement" of the FDCA in the Secretary of Health and Human Services, who in turn delegated that authority to FDA, which is charged with evaluating and approving the applications required to introduce drugs into interstate commerce. *See* 21 U.S.C. §371. In exercising that authority, the Agency may not promulgate regulations that are inconsistent with the governing statute. *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 125-26 (2000) (holding agency, in promulgating regulations, and court, in reviewing regulations, "must give effect to the unambiguously expressed intent of Congress" (citing *Chevron U.S.A. Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837 (1984)).

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In enacting the Drug Price Competition and Patent Term Restoration Act (commonly referred to as the "Hatch-Waxman Amendments" to the FDCA), Congress provided that FDA cannot approve an ANDA if, with certain exceptions, the labeling proposed for the generic drug is not the same as the labeling approved for the listed drug. *See* 21 U.S.C. §355(j)(4)(G); *see also* 21 U.S.C. §355(j)(2)(A)(v) (requiring that ANDAs include information to show the labeling proposed for the generic drug is the same as the labeling approved for the listed drug). Those requirements subsequently were incorporated into FDA's regulations. *See* 21 C.F.R. §314.94(a)(8) (providing that ANDAs must include labeling that is the same as labeling approved for listed drug and must include "[a] statement that the applicant's proposed labeling ... is the same as the labeling of the reference listed drug except for differences annotated and explained under paragraph (a)(8)(iv) of this section"). In addition, Congress prohibited FDA from requiring that ANDAs contain information in addition to that required by §355(j)(2)(A)(i)-(viii), *see* 21 U.S.C. §355(j)(2)(A). The requirements in §355(j) apply to supplemental applications as well. (*See* Brief for the United States as Amicus Curiae, On Petitions for Writs of Certiorari, ("U.S. Petition Brief"), Sup. Ct. Case No. 09-993, p. 13 (citing 21 C.F.R. §314.98(a)(8)(iii); Brief of the United States as Amicus Curiae Supporting Respondents in *PLIVA, Inc. v. Mensing*, Sup. Ct. No. 09-993 (March 2011) ("U.S. Merits Brief"), p. 15.)

b. The Proposed Rule Exceeds FDA's Authority

The revisions FDA proposes to its regulations to require ANDA applicants to submit CBE-0 supplements and change their product labeling to reflect "newly acquired information related to drug safety, irrespective of whether the revised labeling differs from that of the RLD" (proposed rule, 78 Fed. Reg. 67986) are contrary to the requirements of the FDCA and Hatch-Waxman Amendments, and therefore, outside FDA's authority to promulgate. In fact, FDA recognized that permitting differences in ANDA product labeling (other than the exceptions permitted by the statute) is inconsistent with the Hatch-Waxman Amendments at the time it issued the regulations implementing the Act. At that time, FDA emphasized that

> the exceptions to the requirement that a generic drug's labeling be the same as that of the listed drug are limited. The agency will not accept ANDAs for products with significant changes in labeling (such as new warnings or precautions) intended to address newly introduced safety or effectiveness problems not presented by the listed drug. Such labeling changes do not fall within the limited exceptions in sections 505(j)(2)(A)(v) and 505(j)(3)(G) of the act. Moreover, **FDA does not believe that it would be consistent with the purpose of section 505(j) of the act, which is to assure the marketing of generic drugs that are as safe and effective as their brand-name counterparts, to interpret section 505(j)(2)(A)(v) of the act as permitting the marketing of generic drugs with diminished safety or effectiveness and concomitantly heightened labeled warnings.**

54 Fed. Reg. 28872 (July 10, 1989) (emphasis added).

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In fact, FDA rejected a suggestion submitted in response to its proposed rule that ANDA applicants be permitted to deviate from the labeling for the reference listed drug to add contraindications, warnings, precautions, adverse reactions and other safety-related information.

> Except for labeling differences due to exclusivity or a patent and differences under section 505(j)(2)(v) of the act, **the ANDA product's labeling must be the same as the listed drug product's labeling because the listed drug product is the basis for ANDA approval. Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart.** (*See* 54 F.R. 28872 at 28884.) If an ANDA applicant believes new safety information should be added to a product's labeling, it should contact FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised. After approval of an ANDA, if an ANDA holder believes that new safety information should be added, it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

57 Fed. Reg. 17950 (Apr. 28, 1992) (emphasis added).[1] FDA also rejected a recommendation that "FDA accept ANDAs with warnings or precautions in addition to those on the reference listed drug's label, provided that such information was not indicative of diminished safety or effectiveness of the generic drug product." (*Id.*)

> As for accepting ANDAs with additional warnings or precautions, section 505(j)(2)(A)(v) and (j)(3)(G) of the act requires that the applicant's proposed labeling be the same as that of the reference listed drug unless: (1) The labeling differences are due to an approved petition under section 505(j)(2)(C) of the act (otherwise referred to as a "suitability petition"); or (2) the drug product and the reference listed drug are produced or distributed by different manufacturers. (*See* 21 U.S.C. 355(j)(2)(A)(v) and (j)(3)(G).)

Id.

More recently, FDA confirmed that permitting ANDA holders to utilize the CBE-0 procedures would conflict with the statutory requirements. In amicus briefs filed in the Supreme Court in *Mensing*, FDA told the Court that

> supplements are subject to the substantive standards governing applications, so the CBE regulation must be read in conjunction with regulations pertaining

[1] FDA takes the position that the process it utilizes for generic drug manufacturers to provide new safety information to the Agency following product approval that permits FDA to determine whether labeling for both generic and listed drug should be revised "reconciles … conflicting statutory mandates that a generic drug not be misbranded, 21 U.S.C. §352, yet also bear labeling "the same as the labeling approved for the [RLD]," 21 U.S.C. §355(j)(4)(G)). FDA, therefore, also must recognize that changes to labeling by ANDA applicants through a CBE-0 process could render the products misbranded under 21 U.S.C. §352.

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> specifically to generic labeling. Those requirements require a generic drug's labeling to be "the same as the labeling of the [RLD]."

(U.S. Petition Brief, p. 13 (citing 21 C.F.R. §314.98(a)(8)(iii); U.S. Merits Brief, p. 15.) And, of course, the reason the regulations require the labeling to be the "same as the labeling of the RLD" is because that is what the statute requires, as FDA clearly is aware as evidenced by FDA's citation in its amicus brief to 21 U.S.C. §355(j)(4)(G). (U.S. Petition Brief, p. 13; U.S. Merits Brief, p. 15.) Based on the "substantive limitations on generic labeling," FDA told the Supreme Court that it "consistently [has] taken the position that an ANDA holder may not unilaterally change its approved labeling." (*Id.*)

There has not been an amendment to the FDCA regarding approval of ANDAs that changes the original requirements, and FDA cites none in the proposed rule. The citation to the FDCA and the Public Health Service Act ("PHS") as a whole does not identify the authority under which FDA asserts it may issue the proposed regulations.

FDA's proposal to permit ANDA applicants to distribute and post revised labeling submitted via a CBE-0, but not approving that CBE-0 until a change has been approved for the RLD's labeling, is a misplaced attempt to fall within the boundaries established by Congress in the Hatch-Waxman Amendments. However, it places ANDA applicants in the untenable legal position of introducing or delivering for introduction into interstate commerce a generic drug with labeling not approved pursuant to 21 U.S.C. §355(j). FDA does not have the authority to permit, much less require, ANDA applicants to violate federal law.

2. The Proposed Regulations Would Lead to Unwarranted Confusion

The proposed rule requires ANDA applicants to submit CBE-0 supplements revising product labeling and contemporaneously requires distribution of that revised product labeling not only with their products, but also through electronic means and via Dear Health Care Professional Letters. In addition, under the proposed rule, FDA would post the revised labeling either on a dedicated website or on an existing modified website. Currently, uniform safety information provides certainty for patients, doctors, pharmacists and nurses and assures all health care practitioners that they can rely on consistent information to inform their decisions and patient conversations. Identical labels underscore a critical point − once generic medicines pass through extensive FDA review, they are deemed equal to the brand medicine in terms of safety, efficacy, and quality.

The process proposed would create unwarranted confusion not only for ANDA applicants and the manufacturer of the listed drug, but also for consumers, physicians, and other health care providers. It also would lend itself to conclusions that the RLD and its generic counterparts are not therapeutically equivalent and do not possess the same safety and efficacy profiles, causing confusion and subverting both the letter and fundamental intent of the Hatch-Waxman Amendments. There is both the possibility that physicians would receive multiple identical "Dear Health Care Professional" letters for exactly the same label change and that they would

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receive multiple different "Dear Health Care Professional" letters for the same concern. The danger of patients not receiving the medications they need is very real. The primary objective of any change to existing regulations should be the improvement of public safety and health. Confusion is not an ally of that objective.

a. Under the Proposed Rule Numerous Different Product Labels for the Same Drug Will Be in the Marketplace at the Same Time

The proposed rule requires an ANDA applicant to submit a CBE-0 supplement if it "obtains or otherwise receives newly acquired information that should be reflected in product labeling to accomplish any of the [following] objectives":

> (A) To add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling under §201.57(c) of this chapter;
>
> (B) To add or strengthen a statement about drug abuse, dependence, psychological effect, or overdosage;
>
> (C) To add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product;
>
> (D) To delete false, misleading, or unsupported indications for use or claims for effectiveness.

(Proposed rule, 78 Fed. Reg. 67989 (citing 21 C.F.R. §314.70(c)(6)(iii)(A)-(D).)[2]

Upon submission of the CBE-0, ANDA applicants will be required to ship their products with the revised labeling. In addition, ANDA applicants will be permitted to distribute "Dear Health Care Professional" letters regarding the labeling change (proposed rule, 78 Fed. Reg. 67989), and are "expected" to use "available means (e.g., distribution of revised labeling in electronic format to the public) to distribute the revised labeling at the time of the submission of the CBE-0 supplement to FDA …." (Proposed rule, 78 Fed. Reg. 67990.) Upon receipt of the CBE-0, FDA will "promptly" post the information regarding the labeling change on a dedicated website or an existing website. (Proposed rule, 78 Fed. Reg. 67990.) In short, four different routes of distribution of revised labeling submitted by every ANDA applicant, as well as the NDA holder, may be employed simultaneously even while FDA is reviewing the CBE-0 and deciding whether to approve it.

The net effect of multiple ANDA applicants revising labels either simultaneously or within a short period of time of one another[3] will result in multiple, different labels for the same drug

[2] The proposed rule later cites to §314.70(c)(6)(iii)(A)-(E).

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being distributed through four different channels. From its long history of discussing label content with sponsors of NDAs, FDA surely is cognizant that no two people will draft exactly the same words to express even exactly the same concept. And, from its long history of evaluating label content, FDA undoubtedly is cognizant that two people can interpret even identical language in two different ways and surely will interpret different language attempting to express the same concept differently. The end result likely will be the dissemination of multiple product labels, electronic postings, and "Dear Health Care Professional" letters that are not uniform and that do not provide "the same" safety-related information and that will lead to confusion among health care professionals and the public as to the actual safety information contained in the labeling.

Indeed, FDA recognized that "decisions about how to address a safety concern often are a matter of judgment, about which reasonable persons with relevant expertise may disagree, and this may be reflected in different approaches to proposed labeling changes based on newly acquired safety information." (Proposed rule, 78 Fed. Reg. 67991 (citing Guidance on "Drug Safety Information – FDA's Communication to the Public (2007).) Those differences in "judgment" likely will be reflected in various, non-uniform changes to product labeling among the various ANDA holders for a given product, engendering uncertainty and confusion.

FDA acknowledges the likely "concerns about the temporary differences in safety-related labeling for drugs that FDA has determined to be therapeutically equivalent," but minimizes those concerns stating that "health care practitioners are unlikely to review product labeling for each of the generic drugs that may be substituted for the prescribed product …." (Proposed rule, 78 Fed. Reg. 67989.) If it is true that health care practitioners will not review the revised labeling of ANDA products, FDA's stated reason for the proposed rule disappears. How will requiring ANDA holders to submit CBE-0s with revised labeling to reflect purported newly acquired information improve "communication of important drug safety information to prescribing health care providers and the public"? (Proposed rule, 78 Fed. Reg. 67986.)

In contrast, if that statement is not true, (and FDA does not provide any support for its "recognition" that health care practitioners will not review revised labeling but instead "address[es] those concerns" by proposing to establish the dedicated website or modify an existing website to provide the fourth channel of distribution of the different safety-related product labeling), FDA ignores the potential confusion that will result if multiple competing CBE-0 submissions for equivalent generic pharmaceutical products remain published on such a website and available to health care providers and the general public for an extended period of time as FDA reviews all submissions and determines its course of action.

In other words, there are two possible outcomes of having multiple versions of product labels distributed to the public—neither of which is beneficial to public health: (1) The multiple revised labels encouraged by the rule will be ignored by health care practitioners and the public

[3] The reason multiple CBE-0s will be submitted within a relatively short time of the first submission will be discussed below in relation to the potentially massive product liability exposure the proposed rule creates for ANDA applicants.

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(as FDA contends), thereby serving no discernible purpose; or (2) the multiple labels will create unwarranted confusion regarding the safety of the drug and whether generic versions are in fact the same as the innovator, thereby undermining the goals of the Hatch-Waxman Amendments without improving safety.

b. The Proposed Rule Would Create Inconsistency in the Labeling of the RLD and Its Generic Equivalents, thereby Casting Doubt on the Therapeutic Equivalence and Safety Profile of the Products

The importance of consistency in labeling for the RLD and its generic equivalents was recognized by FDA years ago when it proposed the regulations to implement Hatch-Waxman and reiterated in the final rule.

> Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart. (*See* 54 F.R. 28872 at 28884.)

57 Fed. Reg. 17950 (Apr. 28, 1992). Indeed, the recognition dates back even earlier than that, as noted in FDA's amicus briefs filed in the Supreme Court in *Mensing* where it reiterated the importance of consistency in RLD and ANDA labeling.

In its brief at the petition stage, FDA advised the Supreme Court that the requirement that generic drug and RLD labeling be the same "reflects a fundamental premise of the ANDA process that a generic drug can be relied upon as a therapeutic equivalent of its RLD." (U.S. Petition Brief, p. 5 (citing 54 Fed. Reg. 28,884 (1989).) Based on that premise, FDA told the Supreme Court that

> FDA places "a very high priority [on] assuring consistency in labeling," so as "to minimize any cause for confusion among health care professionals and consumers as well as to preclude a basis for lack of confidence in the equivalency of generic versus brand name products."

(U.S. Petition Brief, p. 5 (citing Division of Generic Drugs, FDA, *Policy and Procedure Guide* 37 (1989); *see* 57 Fed. Reg. 17,961 (1992).) FDA again reiterated the importance of maintaining consistency in the labeling of the RLD and ANDA products in its amicus brief filed at the merits stage in *Mensing*. (*See* U.S. Merits Brief, p. 4 (restating in its entirety quoted language).)

The importance of consistency extends beyond the product's labeling to other communications with physicians. For instance, in its amicus brief, FDA told the Supreme Court that a "Dear Health Care Professional" letter "from an ANDA holder could inaccurately imply therapeutic differences between the generic drug and its RLD that do not exist, and therefore be misleading" and explained that "an ANDA holder's letter warning about risks seemingly unique to its product could mislead consumers and providers into believing that the generic drug and RLD were not therapeutic equivalents." (U.S. Petition Brief, pp. 17-18; *see also id*., p. 13 ("an ANDA holder

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unilaterally sending DHCP letters … could have resulted in misbranding of drug"); *id.*, p. 17 (stating "Dear Health Care Professional" letters "sent by a generic manufacturer could potentially affect the perceived therapeutic equivalence of the generic drug and its RLD counterpart").)

ANDA applicants historically have not sent "Dear Health Care Professional" letters to physicians, and in certain instances may be prohibited from doing so. Indeed, they generally do not call on physicians' offices or market their generic drug products to physicians or to the general public. Has FDA considered that the additional cost to ANDA applicants of hiring persons capable of communicating complex technical information to physicians may frustrate Congressional objectives of reducing the costs of generic drugs? Has FDA considered the impact of the cost of the mailings themselves? Has FDA considered the costs and impact associated with the redundancy inherent in its proposal? Has FDA determined the means by which ANDA applicants will determine to whom such "Dear Health Care Professional" letters should be sent or the cost of the services that might be required to identify those persons? Has FDA considered the potential for dilution of the importance of "Dear Health Care Professional" letters that may result if each health care provider is receiving dozens of such communications for every drug product each time there is a label change? FDA should respond to each of those important questions.

Now less than three years after it explained the fundamental premise underlying the "same as" requirement, FDA proposes a change to its regulations that would undermine the "fundamental premise" of the Hatch-Waxman "sameness" requirement and would be in absolute contradiction to the law. And, it does so with no intervening change in the statute and no explanation, much less support, for its proposal. Yet, one can assume that consumers still would be confused today by inconsistent labels or lack "confidence in the equivalency of generic versus brand name products." Those public health issues are no less important to the generic pharmaceutical industry today than they were in 1989—and they also should be no less important to FDA.

3. The Proposed Rule Is Not Supported By Any Empirical Evidence that ANDA Applicants Have Not Complied with Their Regulatory Obligations Historically or that the "Incentives" for Them to Comply with Those Obligations Have Been Altered in Light of Recent United States Supreme Court Decisions

In the proposed rule, FDA discusses two recent decisions from the United States Supreme Court, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011), and *Wyeth v. Levine*, 555 U.S. 555 (2009), and speculates that "[t]he *Mensing* decision alters the incentives for generic drug manufacturers to comply with current requirements to conduct robust postmarketing surveillance, evaluation, and reporting, and to ensure that the labeling for their drugs is accurate and up-to-date." (Proposed rule, 78 Fed. Reg. 67988.) Yet, FDA does not provide any empirical evidence that demonstrates either that (1) ANDA applicants have not complied with their postmarketing obligations historically, or (2) the "incentives" for ANDA applicants to comply with postmarketing

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obligations have been altered. Further, FDA has not offered any evidence to demonstrate a change is warranted or that the current system has not operated successfully or will not continue to operate successfully.[4]

The Supreme Court's decision in *Mensing* did not change the regulatory framework applicable to ANDA applicants. Lawsuits filed against ANDA applicants that alleged inadequacies in product labeling before *Mensing* was decided were based on the false premise that ANDA applicants could change product labels unilaterally. ANDA applicants, cognizant of the federal regulatory requirements, knew their product labeling had to conform to the NDA product labeling. FDA's proposed rule implies that ANDA applicants were incentivized to fulfill their regulatory obligations only because of the unwarranted state-law tort lawsuits filed against them; however, FDA does not supply any support for that implication. Nor does FDA supply information to support an assertion that ANDA applicants have been less compliant with their regulatory obligations since *Mensing* was decided more than two years ago.

The proposed rule is devoid of any evidence that the same group of manufacturers suddenly now lack incentives to comply with their existing obligations, or that those companies are, in fact, non-compliant. Indeed, if lack of compliance were truly an issue, the typical response would be enforcement, not additional rules that an (allegedly) non-complying group likely would ignore. FDA appears to have created an issue—lack of incentives leading to lack of compliance—from whole cloth.

It would seem prudent that FDA, before instituting a massive (unauthorized) overhaul to the regulatory framework for labeling generic drugs that has worked so effectively for almost 30 years, has made greatly needed (and often life-saving) low-cost medications available to the American population, and has saved federal and state governments and the public billions of dollars in the process, should conduct a study to determine whether ANDA applicants are more compliant or less compliant with their regulatory obligations as a result of the Supreme Court's decisions in *Mensing* and *Mutual Pharm. Co., Inc. v. Bartlett*, 133 S. Ct. 2466 (2013), rather than premising its proposed rule change on an unsupported hypothesis that the rulings have somehow dis-incentivized generic drug manufacturers.

4. The Proposed Rule Is Based on a Flawed Premise that ANDA Applicants Receive or Possess Sufficient Data to Propose and Support Safety-Related Changes to Product Labeling

The proposed regulations would require ANDA applicants to submit a CBE-0 to update product labeling to reflect "newly acquired information" that meets the criteria in 21 C.F.R. §314.70(c)(6)(iii)(A) through (c)(6)(iii)(D). (Proposed rule, 78 Fed. Reg. 67989.) In the proposed rule, FDA states

[4] Also, FDA's statement about "current requirements" for "robust" "postmarketing surveillance" is puzzling as those terms do not appear in any applicable statute or regulation, and FDA does not define the terms.

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> [a]pplication holders must promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers, and comply with applicable reporting and recordkeeping requirements (see §§314.80(b), 314.98(a), and 600.80(b)).

(Proposed rule, 78 Fed. Reg. 67986.) In addition, FDA states that "all application holders, including ANDA holders are required to conduct surveillance, evaluation, and reporting of postmarketing adverse drug experiences and, if warranted, to propose revisions to product labeling." (Proposed rule, 78 Fed. Reg. 67989.)

a. Current Regulations Require ANDA Applicants to Comply with the "Reporting and Recordkeeping" Requirements of 21 C.F.R. §314.80

As an initial matter, FDA's statement that "all application holders, including ANDA holders are required to conduct surveillance, evaluation, and reporting of postmarketing adverse drug experiences and, if warranted, to propose revisions to product labeling," is not supported by the language of the current regulations. Nowhere in the regulations is there a requirement for either NDA or ANDA applicants to search the world's scientific literature but rather to review and report information "obtained or otherwise received." It long has been understood by the Agency and NDA and ANDA holders that the innovators possess more comprehensive scientific data on their products than ANDA manufacturers and that having multiple ANDA manufacturers repeat all the pharmacovigilance activities of NDA holders, who possess more complete data, would be inefficient, redundant, and wasteful. It also would increase the costs of generic drugs.

Moreover, §314.98 does not require ANDA applicants to comply with all subsections of §314.80 ("Postmarketing reporting of adverse drug experiences"), but rather provides that ANDA applicants "shall comply with the requirements of 314.80 *regarding the reporting and recordkeeping of adverse drug experiences*." 21 C.F.R. §314.98(a) (emphasis added). The "reporting and recordkeeping" requirements in §314.80 are in §314.80(c) ("*Reporting requirements*") and §314.80(i) ("*Recordkeeping*"). Indeed, the regulation FDA cites for its statement is §314.80(b), which, by its terms, applies to NDAs. Specifically, that section states:

> (b) *Review of adverse drug experiences*. Each applicant having an approved application under 314.50 or, in the case of a 505(b)(2) application, an effective approved application, shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers. Applicants are not required to resubmit to FDA

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> adverse drug experience reports forwarded to the applicant by FDA; however, applicants must submit all follow-up information on such reports to FDA. Any person subject to the reporting requirements under paragraph (c) of this section shall also develop written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA.

21 C.F.R. §314.80(b). Approved applications under §314.50 and 505(b) are NDAs, not ANDAs. The only portion of §314.80(b) applicable to ANDAs is the last sentence requiring the development of "written procedures for the surveillance, receipt, evaluation, and reporting of postmarketing adverse drug experiences to FDA" for "any person subject to the *reporting requirements under paragraph (c)*" as ANDA applicants are by virtue of 21 C.F.R. §314.98.

In short, FDA's statement in the proposed rule regarding ANDA applicants' postmarketing obligations is not supported by the language of its regulations.

b. ANDA Applicants Do Not Generally Receive or Possess Necessary Data to Propose and Support Safety-Related Changes to Product Labeling

The trigger for submitting a CBE-0 with revised safety-related labeling is the acquisition of "new information" that "causes information in labeling to be inaccurate …." (Proposed rule, 78 Fed. Reg. 67986.) "Newly acquired information" is defined as "data, analyses, or other information not previously submitted to the agency, which may include (but are not limited to) data derived from new clinical studies, reports of adverse events, or new analyses of previously submitted data (e.g., meta-analyses) if the studies, events or analyses reveal risks of a different type or greater severity or frequency than previously included in submissions to FDA." 21 C.F.R. §314.3(b).

There are several reasons NDA holders—rather than ANDA applicants—are in the best position to update product labeling. First, and perhaps foremost, only NDA holders know what "data, analyses, or other information [has] not [been] previously submitted to [FDA]." ANDA applicants do not have access to the original clinical trial data, they do not have access to any post-approval clinical trial or post-marketing study data, they do not have access to the information the NDA holder has submitted to FDA previously, they do not have access to what information FDA has obtained independently, and they do not have access to what information any other manufacturer or outside source may have submitted to FDA. In fact, as FDA is aware, the statutory provisions do not permit submission of an ANDA where clinical studies are necessary to establish safety and efficacy of the product. *See* 57 Fed. Reg. 17960 (Apr. 28, 1992) ("As stated in section §505(j)(2)(C), if clinical investigations are needed to establish a product's safety or effectiveness, that product is not suitable for an ANDA."). Moreover, it would be extremely rare for "new clinical studies" to be conducted for a drug already eligible for generic versions. And, if any such data did exist, the ANDA applicant would not be the company/entity with the data. Similarly, ANDA applicants would not have a new analysis of existing clinical data. Although ANDA applicants could reanalyze adverse event data, they

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would be doing so without the benefit of clinical data submitted to FDA. Moreover, if ANDA applicants were reanalyzing adverse event reports submitted by other companies, it would be doing so without the benefit of all the data on the Medwatch form—as all that data is not available in the electronic adverse event database. As a result, the initial premise of the proposed rule is flawed.

Second, as FDA recognized in the proposed rule,

> interpretation of postmarketing safety data is complex, involving analysis of post approval clinical data, detailed review of adverse drug experience reports in the context of relevant clinical studies, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse event, and other relevant information.

(Proposed rule, 78 Fed. Reg. 67991.) NDA holders and FDA possess the most data and are best suited to undertake that analysis. ANDA applicants do not have access to the various sources of information FDA concedes are necessary to interpret postmarketing data. As such, they are unable to interpret the newly acquired data they may obtain to determine if the data or other information "causes information in labeling to be inaccurate…" (Proposed rule, 78 Fed. Reg. 67986.)

At the time Hatch-Waxman was enacted, it was recognized that ANDA applicants do not possess the data or resources necessary to interpret and evaluate postmarketing data and information they receive. During a meeting of the Health and the Environment Subcommittee of the House of Representatives Committee on Energy and Commerce, on July 25, 1983, the then-Deputy Commissioner of FDA, Mark Novitch, M.D., explained to the subcommittee that the first opportunity to examine low incidence reactions to any pharmaceutical product is following initial marketing of the new drug. (Hearing Transcript, p. 7.) He further testified that during that initial marketing period all adverse events would be reported to the innovator manufacturer, who is familiar with the preapproval testing and, therefore, in the best position to evaluate the adverse reactions. (*Id.*) Dr. Novitch explained that while it could be argued that

> generic drug firms are required to report adverse drug reactions to FDA, and that FDA can therefore evaluate their significance[,] [] most adverse drug reaction reports are to some extent evaluated by the firm receiving them, and the quality and timeliness of that review is important to the process.

(*Id.*) He went on to explain that, as they do today, only unexpected adverse reactions or clinical failures must be reported to FDA within 15 working days and all others are submitted quarterly during the first year. (*Id.*) Dr. Novitch also recognized the importance of having adverse reaction reports evaluated by those familiar with the pre-existing data:

> If adverse reaction reports were received by firms unfamiliar with the clinical trials, and, because of the nature of their business, lacking ties with the research

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> community, we are concerned about the adequacy of the reports we would receive. The holder of the pioneer NDA is frequently of considerable help to FDA in identifying adverse reaction trends and other drug effects bearing on the safe and effective use of a newly developed drug therapy.

(*Id.*)

The generic drug industry has grown, and its members are diverse in size and resources. Yet FDA still recognizes that NDA holders have the most complete data for analyzing safety data. In the proposed rule, FDA states that "FDA's analysis of whether the labeling change proposed by an ANDA holder in a CBE-0 should be approved (and required for inclusion in the labeling of all versions of the drug) would benefit from the views of the NDA holder …" because "[t]he NDA holder has full access to the data upon which the RLD was approved and, in most cases, has substantial knowledge about the postmarketing experience for the drug product." (Proposed rule, 78 Fed. Reg. 67991; *see also* U.S. Petition Brief, p. 22 (acknowledging that generic drug manufacturers do not possess "knowledge as comprehensive as FDA's or the NDA holder's" and requiring them to develop that knowledge raises "preemption questions").)

Reglan provides a real world example. Reglan, the RLD for metoclopramide, was approved by FDA in December 1980. Since then, Reglan tablets have been indicated as short-term (4 to 12 weeks and 2 to 8 weeks respectively) therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy and for the relief of symptoms associated with acute and recurrent diabetic gastric stasis.

Litigation involving the prescription medication Reglan and its alleged risk of causing tardive dyskinesia or other movement disorders dates back almost three decades. After the first case, additional cases were filed from time to time, but thousands of lawsuits involving metoclopramide were filed only after FDA announced a change for the product's labeling in 2009. The crux of plaintiffs' claims during the course of the Reglan litigation was that the warning in the Reglan/metoclopramide labeling that "[e]xtrapyramidal symptoms, manifested primarily as acute dystonic reactions, occur in approximately 1 in 500 patients treated with the usual adult dosages of 30 to 40 mg/day of metoclopramide" (the "1-in-500 warning") understated the risk of developing movement disorders from long-term use; i.e., over 12 weeks, of the drug. The reason for the targeted allegation is simple: The Reglan/metoclopramide labeling included a detailed warning regarding the risk of developing tardive dyskinesia, a warning that was placed in the labeling in 1985 (five years after Reglan was approved) as a result of the postmarketing data generated during the years immediately following Reglan's approval. *See* FDA Drug Review, Post-Approval Risks 1976-85 ("GAO Review"), GAO, April 1990, p. 111 (identifying and documenting labeling changes to approved drugs implemented by FDA following initial approval based on discovery of potential risks after initial marketing). As a result, in March 1985, FDA requested the NDA holder to change Reglan's package insert to include a warning that tardive dyskinesia may develop in patients treated with metoclopramide. That change was made in May 1985. The May 1985 labeling was deemed "approvable" by FDA

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on August 20, 1985, and was distributed by Robins, who held the NDA at that time, with a Dear Doctor Letter in November 1985.[5]

The change FDA implemented to the Reglan/metoclopramide labeling in 2009 did not significantly change the pre-existing tardive dyskinesia warning. Rather, it merely highlighted the warning in a black box because neither physicians nor patients were following the labeled recommendation for limited duration of therapy. Most importantly, the 2009 change did not change the 1-in-500 warning language—it remains in the labeling today. Yet, following the 2009 changes, thousands of lawsuits against Reglan/metoclopramide manufacturers were filed around the country, the majority of which continued to allege that the 1-in-500 warning was inadequate.

ANDA applicants that manufacture metoclopramide do not have the source data for the 1-in-500 warning and, as a result, could not, and still cannot, ascertain whether that language should be changed based on postmarketing data they have received. Ironically, FDA's 2009 change demonstrates that no "newly acquired information" exists to support a change in the 1-in-500 warning. Nonetheless, *Mensing* was a case involving metoclopramide, and the dissent in the Supreme Court and now even the FDA lament plaintiff's inability to sue the generic manufacturers over their "failure" to change that language.

As FDA recently recognized, "genuinely new information about drugs in long use (as generic drugs typically are) appears infrequently …." (U.S. Merits Brief, pp. 34-35; *see also* U.S. Petition Brief, p. 16 (noting situations in which ANDA applicants receive information that might indicate the need for a labeling revision "arise infrequently, and when they do, there tend to be unique, fact-specific considerations at issue").) That same recognition was noted by the Office of Generic Drugs years ago in its Manual of Policies and Procedures, MAPP 5240.8, "Handling

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[5] The warning was as follows:

> **Tardive Dyskinesia**
>
> Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with metoclopramide. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients (sic) are likely to develop the syndrome. Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase with the duration of treatment and the total cumulative dose. Less commonly, the syndrome can develop after relatively brief treatment periods at low doses; in these cases, symptoms appear more likely to be reversible. There is no known treatment for established cases of tardive dyskinesia although the syndrome may remit, partially or completely, within several weeks-to-months after metoclopramide is withdrawn. Metoclopramide itself, however, may suppress (or partially suppress) the signs of tardive dyskinesia, thereby making (sic) the underlying disease process. The effect of this symptomatic suppression upon the long-term course of the syndrome is unknown. Therefore, the use of metoclopramide for the symptomatic control of tardive dyskinesia is not recommended.

(2002 Reglan Package Insert.)

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of Adverse Experience Reports and Other Generic Drug Postmarketing Reports" (November 1, 2005). The stated purpose of the MAPP is to "define the procedure for handling any adverse experience report (AER) or other postmarketing reports received by the Office of Generic Drugs (OGD) concerning the use of a generic drug product." (*Id.*) In the "Background" section of the MAPP, OGD noted:

> Generally, OGD receives few AERs or similar reports since the reports may not specify a generic manufacturer for the drug product. Furthermore, the safety profile of a particular drug is usually well-known before generic versions are approved. Therefore, AERs associated with a generic drug are less likely to be reported.

(*Id.*) That MAPP remains in effect today.[6] The conclusions in the MAPP that ANDA applicants receive few reports of adverse events because those events generally are reported to FDA directly or to the NDA holder is discernible from FDA's adverse event report database. In most instances, because it is unknown what company's product was dispensed when a prescription was filled, reports of adverse events are sent directly to FDA or to the NDA holder and not an ANDA applicant. In fact, often the reports of adverse events reported by ANDA applicants to FDA are generated from lawsuits that have been filed. In many instances, those same events were reported to the NDA holder or FDA prior to the initiation of the lawsuit. Such sparse, suspect data is not susceptible to scientific analysis and should not be the basis of label changes.

In short, the proposed rule imposes an undue and irrational burden—it would create an obligation to provide warnings that cannot be properly substantiated and that may run afoul of the misbranding requirements of the FDCA. While the NDA holder and FDA can make their decisions on warnings based on a full safety data set in the NDA, ANDA holders do not have access to that data, and there may be countervailing risks associated with modifying warnings without knowledge of the entire data set. Indeed, FDA recognized decades ago that the well-being of patients depends, in part, upon the delicate balance between warning and over-warning and that generic drug companies are not in a position to know whether risk information already is adequately described in a package insert because they do not possess all the relevant data. The health and safety of persons using generic pharmaceutical products is no less important today than it was decades ago. Risk information must be grounded in science, brand and generic products must contain the same warnings, and patients who desperately need pharmaceutical products should not be inappropriately discouraged from taking them.

In fact, FDA raised the broader concern about unsubstantiated new warnings during rulemaking in 2008, where it sought to limit NDA holders' ability (and obligation under tort law) to provide new warnings without agency approval:

[6] *See* http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/default.htm.

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> Explicitly requiring that CBE supplements are utilized in a manner proposed by this amendment ensures that only scientifically justified information is provided in the labeling for an approved product. Exaggeration of risk, or inclusion of speculative or hypothetical risks, could discourage appropriate use of a beneficial drug, biologic, or medical device or decrease the usefulness and accessibility of important information by diluting or obscuring it. As FDA has stated, labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance. *See, e.g.*, ''Write it Right: Recommendations for Developing User Instruction Manuals for Medical Devices Used in Home Health Care'' (August 1993) (http://www.fda.gov/cdrh/dsma/897.pdf) (''Overwarning has the effect of not warning at all. The reader stops paying attention to excess warnings.'') ....
>
> Before approving an NDA, BLA, or PMA, the FDA undertakes a detailed review of the proposed labeling, allowing only information for which there is scientific basis to be included in the FDA-approved labeling. Under the act, the Public Health Service Act (PHS Act), and FDA regulations, the agency makes approval decisions, including the approval of supplemental applications, based on a comprehensive scientific evaluation of the product's risks and benefits under the conditions of use prescribed, recommended, or suggested in the labeling. *See, e.g.*, 21 U.S.C. §355(d); 42 U.S.C. §262; 21 U.S.C. §360e(d)(2). FDA's comprehensive review is embodied in the labeling for the product which reflects thorough FDA review of the pertinent scientific evidence and communicates to health care practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively.

73 Fed. Reg. 2848, 2851 (2008) (emphasis added).

ANDA applicants do not have access to the full data in the NDA and FDA cannot share much of the data. For ANDA applicants to participate as fully as an NDA holder in FDA discussions on labeling changes, the ANDA holder will need to be as informed as the NDA holder itself. However, that information almost certainly would include proprietary data. As a result, ANDA holders cannot properly substantiate new warnings and such unsubstantiated warnings could misbrand the product under section 21 U.S.C. §352.

Furthermore, FDA's statement that "in the current marketplace, in which approximately 80 percent of drugs dispensed are generic and, as we have learned, brand name drug manufacturers may discontinue marketing after generic drug entry, FDA believes it is time to provide ANDA holders with the means to update product labeling to reflect data obtained through postmarketing surveillance …" (proposed rule, 78 Fed. Reg. at 67988) is based on flawed reasoning. It presumes that just as there usually is only one NDA holder, there also is only one ANDA holder for any particular generic drug. That is not the case. For virtually every generic drug there are multiple manufacturers. Grouping total market share of all generic drug manufacturers for a particular drug ignores the reality of the marketplace. While one generic drug manufacturer may

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have a larger share of the market than another generic drug manufacturer, other than during periods of exclusivity, seldom does one generic manufacturer control 80% of the market for any given drug. Therefore, it is improper to assume that any one generic manufacturer receives 80% of the adverse event data following generic entry into the market. Instead, each generic manufacturer may possess only a small percentage of the anecdotal data and none of the clinical data.

c. The Proposed Rule Creates Uncertainty and Raises Myriad Questions

There is a fundamental question whether any ANDA applicant can submit a CBE-0, for the reason that such a submission requires scientific justification, and arguably, generic companies do not possess sufficient data for that justification. Indeed, it is reasonable to question FDA's authority under the FDCA to require ANDA holders, who by definition do not possess all the safety data on their pharmaceutical products, to distribute safety information known to have been developed with less than all the available data. Nonetheless, once a CBE-0 has been submitted by one ANDA applicant, that submission raises other important questions. For instance, do other ANDA applicants then possess "new information"? Should those other companies implement the label change of the company that has submitted the CBE-0, or should they implement the labeling they feel is most appropriate based upon their multiple interpretations of the same data? If the other ANDA applicants do not possess the "new information" until after FDA has reviewed and ruled on the CBE-0, are the other ANDA applicants that then possess "new information" expected to make their own judgments about the "new information" and submit separate CBE-0s to reflect their understandings of the data? If a label change posted to a website is "new information" to another ANDA applicant, is there any reason that company should defer to the posting company's assessment as to how the label should be changed as opposed to coming to its own conclusion and posting its own version of the label? Will the companies submitting the CBE-0s and the FDA make all the data supporting the label change available to all the other companies so that they can make their own assessments as to the appropriateness of the label change? Does FDA agree that ANDA applicants that did not submit the CBE-0 may have analyzed the same data already and concluded that a label change is not warranted? If so, does FDA intend to involve all manufacturers in discussions of label changes or just the NDA holder and the company that submitted the CBE-0? Presently, when issues related to a potential label change arise, FDA shares all data and information with the NDA holder, the only entity able to make a label change. If the proposed rule is implemented and all manufacturers are able to make label changes, and might have civil liability for not doing so, will the FDA share with all manufacturers all data and information relevant to a potential label change? Simply stated, the proposed rule creates uncertainty and potentially even chaos, and provides no guidance on how to resolve the questions that are almost certain to arise. Those are important questions FDA should address. However, it is unlikely FDA can address them in a manner that resolves the major concerns set forth in these comments.

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5. The Proposed Regulations Would Greatly Increase the Cost of Generic Pharmaceutical Products

To comply with the requirements FDA is proposing will necessitate a change in the generic pharmaceutical industry's business model. That change comes at a cost.

As FDA recognized just a few short years ago, generic drug manufacturers do not possess "knowledge as comprehensive as FDA's or the NDA holder's" (U.S. Petition Brief, p. 22), because, in the words of Dr. Novitch in 1983, while generic pharmaceutical companies "are production oriented, the research-based companies are research oriented" (Dr. Novitch testimony, Hearing transcript, p. 10). For that reason, and because the NDA sponsor has the clinical data associated with any particular pharmaceutical product, ANDA applicants are ill-equipped to evaluate any data or information received to determine whether any "safety-related" labeling change is necessary or warranted. To comply with FDA's proposed rule, some ANDA applicants will need to retool their businesses and take on additional infrastructure obligations that will necessarily increase the cost of generic drugs.

In the proposed rule, FDA comments that the generic drug industry has matured since enactment of the Hatch-Waxman Amendments. While it is true that there are global generic drug companies, it also is true that there are many small generic drug companies that distribute only a few products. The Hatch-Waxman Amendments have allowed for tremendous competition among pharmaceutical companies to the financial benefit of the federal government, state governments, and the general public through a regulatory regime that allows small generic companies to prosper so long as they can profitably sell products that are the same as their branded counterparts. Some of those companies can license a product, contract for its manufacture, contract for the handling of its adverse event reports, and sell their drugs on very small margins. The proposed rule threatens the existence of such companies. How would such a company know, for example, that the supposed incidence of tardive dyskinesia in patients taking metoclopramide is greater than 1-in-500, when even the brand-name drug manufacturer disputes that claim? Yet, the generic drug manufacturer who is providing a tremendous benefit to the government and to the public by selling that product could be subject to massive litigation that threatens its very existence at the whim of plaintiffs' attorneys because under the proposed regulations, they theoretically could have submitted a CBE-0 to change their label. Every small generic drug manufacturer that is driven from the market, decreases competition and, concomitantly, increases costs.

Even for established generic pharmaceutical companies, the proposed rule could give rise to new and increased obligations that would necessitate hiring new employees; promulgating new internal guidelines, policies, and procedures; and adding internal regulatory scrutiny over other ANDA holders' proposed label changes. Companies seeking to minimize their future potential product liability exposure will need to monitor the proposed website where all CBE-0 submissions will be posted pending approval, and will need to undertake an internal review immediately any time another ANDA holder submits a CBE-0 for a product they manufacture to determine if they should make a similar label change. Even where a manufacturer submits a

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CBE-0 first, and then subsequently other ANDA holders submit their own CBE-0 changes, that manufacturer may well continually evaluate the other proposed label changes to determine if and how they vary, and evaluate whether to incorporate any of the language from other CBE-0 submissions into an amended or supplemental CBE-0, despite the fact that each CBE-0 will be based upon less data than that possessed by the NDA holder. And, of course, with multiple competing and varying ANDA holders' labeling being distributed with product and publicized to medical providers and patients, health care providers and patients may be confused as described in more detail above.

6. The Proposed Regulations Would Open the Generic Drug Industry to Unwarranted State-Law Mass Tort Litigation and Potential Liability

The goal of the proposed rule to create "parity" among NDA and ANDA applicants in the realm of state-law tort liability is transparent and evidenced by FDA's statement that "[i]f this proposed regulatory change is adopted, it may eliminate the preemption of certain failure-to-warn claims with respect to generic drugs." (Proposed rule, 78 Fed. Reg. 67989.) Providing access to the courts, however, is not an appropriate basis for FDA rulemaking. Moreover, it is unclear that FDA has considered the magnitude of the state-law tort lawsuits to which it will expose all generic pharmaceutical manufacturers, as well as the manufacturers of the brand-name drugs—whether the lawsuits have merit or not.

a. Providing Access to the Courts Is Not an Appropriate Basis for Agency Rulemaking

FDA states that "[a]s a result of the decisions in *Wyeth v. Levine* and *PLIVA v. Mensing*, an individual can bring a product liability action for failure to warn against an NDA holder, but generally not an ANDA holder, and thus access to the courts is dependent on whether an individual is dispensed a brand name or generic drug." (Proposed rule, 78 Fed. Reg. 67988.) That statement is a misguided and inappropriate basis for issuing the proposed rule.

It is not a federal agency's place to provide "access to the courts," whether state or federal, for individuals. Indeed, FDA has recognized that concept for decades:

- "Tort liability cannot be a major consideration for FDA which must be guided by the basic principles and requirements of the act in its regulatory activities." 63 Fed. Reg. 66378, 66383 (Dec. 1, 1998).
- "It is not the intent of FDA to influence the civil tort liability of the manufacturer or the physician." 44 Fed. Reg. 37434, 37437 (June 26, 1979).
- "[W]hether particular labeling may alter a manufacturer's liability in a given instance cannot be considered as a dispositive factor by the Commissioner in reaching a decision." 42 Fed. Reg. 37636, 37637 (July 22, 1977).

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FDA should not now insert itself into the realm of civil tort liability—it simply is not the Agency's place to do so.

In addition, whether an individual's pharmaceutical prescription is filled with a product approved under an NDA or a product approved under an ANDA is a function of state law. More specifically, the substitution laws in effect in all 50 states either permit or require pharmacists to substitute a generic version of a pharmaceutical product for its brand-name alternative. Those substitution laws were passed by the respective state legislatures and can be changed by those same legislatures. As a result, an individual's ability to litigate a state-law tort lawsuit is conditioned on a pharmacy dispensing a product approved under an NDA versus a product approved under an ANDA and that dispensing is a function of state law and not judicial decisions of the United States Supreme Court.

b. The Proposed Rule Is Devoid of Any Analysis of the Impact that Providing Access to the Courts Will Have on the Generic Industry

The proposed rule does not include any analysis of the impact that "access to the courts" necessarily would have on the generic drug industry. Certainly, generic drug manufacturers would be faced with the question of whether it made economic sense to continue manufacturing certain generic drugs with high litigation risk profiles, or undertaking to produce generic version of such high-risk pharmaceuticals. As generic drug manufacturers abandon the marketplace, drug prices likely will rise, fewer generic drugs may be brought to market, and drug shortages may be exacerbated, undermining the entire rationale for Hatch-Waxman. That outcome highlights both a fatal flaw of the proposed rule and that the impact of access to the courts needs to be studied.

A survey of lawsuits involving pharmaceutical products in recent years would show that the vast majority of those lawsuits are filed *following* a change to a pharmaceutical product's labeling and not that the lawsuits *prompted* the change. Again, Reglan is a real-world example. Although there were a handful of lawsuits filed involving Reglan, beginning in the late 1980s and continuing through the 2000s, it was not until a change was made to Reglan's label in 2009 that thousands of lawsuits were filed within months of the label change. Ironically, the change to the labeling in 2009 *did not* change the part of the label that had been the basis of the lawsuits during the preceding two decades. Indeed, that language remains in the label today. Another example is the change in the pregnancy category rating for Paxil from C to D. Many hundreds of lawsuits followed that label change. Similarly, the hormone therapy litigation was spawned in large part by the label changes that followed publication of the Women's Health Initiative studies.

That fact, alone, counsels that the real-world effect of a manufacturer's submission of a CBE-0 supplement to update labeling to add what inevitably would be scientifically unsubstantiated safety-related information likely will result in the filing of hundreds, if not thousands, of lawsuits. The impact will be magnified by the scenario FDA is proposing to create. The potential flood of products liability litigation against generic pharmaceutical manufacturers

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ultimately will drive the smaller companies from the market and increase the cost of generic medications, which FDA has not accounted for or addressed in its cost impact analysis.

Once the first manufacturer of a generic pharmaceutical submits a CBE-0 supplement, others are likely to follow shortly thereafter for the simple reason that any manufacturer that does not file its own CBE-0 supplement after the first is filed, will open itself up to lawsuits. Yet, as FDA recognized, "decisions about how to address a safety concern often are a matter of judgment, about which reasonable persons with relevant expertise may disagree, and this may be reflected in different approaches to proposed labeling changes based on newly acquired safety information." (Proposed rule, 78 Fed. Reg. 67991 (citing Guidance on Drug Safety Information—FDA's Communication to the Public (2007).) And, as discussed above, those differences in judgment will lead to differences in language. Ultimately, FDA will disapprove all proposed labeling changes, or it will adopt one, which under the proposed rule the NDA holder will implement, followed, within 30 days, by the ANDA applicants. The manufacturers then will be sued for not proposing the language FDA ultimately adopted.

The process FDA proposes likely will lead to one or more of the following scenarios:

- If the first ANDA applicant's proposal is accepted, every other ANDA applicant that either did not submit its own CBE-0 or that submitted a CBE-0 with different language will be subject to state-law tort suits (that would include the NDA holder as well);
- If a proposal submitted by an ANDA applicant following the first ANDA applicant's submission is accepted, the first ANDA applicant and every other ANDA applicant that either did not submit its own CBE-0 or that submitted a CBE-0 with different language will be subject to state-law tort suits (that would include the NDA holder as well);
- If FDA rejects the proposals submitted by all applicants and instead adopts its own language, all applicants will be subject to state-law tort suits (that would include the NDA holder as well); and
- In each instance, all manufacturers will be subject to state-law tort suits for not making a change earlier.

Under each scenario, plaintiffs will use FDA's rejection of an applicant's proposed language as "evidence" that the labeling was inadequate, even where the ANDA applicant submitted a CBE-0 proposing updated language. The only scenario where applicants may be relieved of potential state-law liability is if FDA rejects all proposals and determines that no change is warranted.

In reality, FDA's proposal will not create "parity," it will create lawsuits—lawsuits against both the NDA holder and ANDA applicants.

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7. The Proposed Regulation Fails to Justify Use of the CBE-0 Process or to Explain Why FDA Cannot Achieve its Objectives within the Bounds of Existing Law

Since enactment of the Hatch-Waxman amendments, generic pharmaceutical companies have played a vital role in the process of ensuring that drugs they manufacture and sell are safe and effective for the approved indications set forth in the product labeling. They have done so by manufacturing those drugs properly, by satisfying their pharmacovigilance responsibilities, and by fulfilling their regulatory responsibilities to conform their drug labeling to the labeling of the RLD. Indeed, FDA recently confirmed as much in its February 27, 2014, letter to Energy and Commerce Health Subcommittee Chairman Joe Pitts: "The proposed rule neither cites nor is based on evidence that generic drug manufacturers are not submitting to FDA required reports of spontaneous adverse event reports that they receive." Nonetheless, FDA has proposed to allow safety information to enter the marketplace that is based upon less than the totality of the scientific data—without any objective evidence that the present process is not working.

Generic drug manufacturers do not possess the proprietary clinical data of innovator companies. While generic companies support processes through which they expeditiously share their data with FDA so that FDA can make appropriate labeling decisions, they also believe the public health is best served by not rushing new labeling to the marketplace that has neither been reviewed by FDA nor by the innovator company. GPhA's members support prompt transmission to FDA of data generic pharmaceutical companies perceive to be "new." Indeed, as FDA recently acknowledged, generic companies provide such data to FDA in fulfillment of their existing regulatory obligations. However, FDA is in possession of the most complete data set of safety information for any individual drug or class of drugs, and is best positioned, in consultation with the innovator, to decide the most appropriate course of action in light of such "new" data. Any proposed changes to existing processes must not lead to a system that places multiple, non-uniform product labels in the market at the same time, or to a system that sacrifices scientific integrity for expediency.

To the extent an initial evaluation of the data submitted by an ANDA applicant warrants widespread dissemination to consumers and health care professionals, FDA can provide that information through the same means it has employed for years—health advisories and health alerts. The message and information would be uniform, it would be based on a complete set of information, and it would alleviate the confusion that surely would accompany differing messages from different manufacturers of the same drug. Moreover, it would continue to provide the consuming public with confidence that generic versions of the brand-name drug are as safe and effective as the brand-name counterpart, thereby serving the Congressional and statutory goals of the Hatch-Waxman Amendments.

8. Conclusion

Monitoring adverse experiences and updating safety-related information on pharmaceutical product labeling is not a simple subject today, just as it was not a simple subject when Hatch-

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Waxman was enacted. As Dr. Novitch explained to the Health and the Environment Subcommittee of the House of Representatives Committee on Energy and Commerce in 1983, "we are not dealing with a simple subject that lends itself to an easy solution." (Hearing transcript, p. 8.) "[T]he difference between the handling of adverse reactions by a generic company and a major research-based company—I think you have to understand and you do understand that the nature of the business is different. The generic companies are production oriented, the research-based companies are research oriented and if I were in a generic firm collecting adverse experience I would bundle it all together and send it in. I would send everything for fear of not wanting to omit anything." (Hearing transcript, p. 10.) In the three decades since Hatch-Waxman was enacted the business model of brand-name pharmaceutical companies and generic pharmaceutical companies has not changed; generic pharmaceutical companies are production-based, a model recognized and endorsed by Hatch-Waxman, and brand-name pharmaceutical companies are research-based, a model also recognized and endorsed by Hatch-Waxman.

The proposed rule is an attempt by FDA to provide people with a means to file lawsuits—a matter that should be of no concern to FDA. It strays from what should be a matter of concern to FDA—furthering Hatch-Waxman's goals of making safe and effective drugs available to consumers at affordable prices. Patients and healthcare practitioners must continue to have access to consistent, transparent information in order to best inform treatment decisions. The FDA's rule as presently drafted would severely undermine those goals.

FDA's proposed rule blindly imposes requirements on ANDA applicants to update their product labeling based on "newly acquired information" and provides a mechanism (with its own flaws) to accomplish that goal but ignores reality—without the data and background information to support a proposed change, ANDA applicants either will submit CBE-0s that cannot be scientifically substantiated, or will forgo submitting CBE-0s for lack of information, neither of which advance any public health goal.

GPhA and its members, dedicated to producing and making available safe and effective generic pharmaceutical products, are concerned that FDA's proposed rule, if implemented, will result not in the dissemination of new safety-related information, but rather in the dissemination of multiple, confusing, and often times unsupported, changes to pharmaceutical product labeling. In an area where public health and patient safety are the primary concern, the end result is destined to cause more harm than good.

Respectfully submitted,

Ralph G. Neas
President and CEO

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