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Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
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CITIZEN PETITION

This petition is submitted under 21 C.F.R. § 10.30 by Public Citizen, a consumer organization with more than 225,000 members and supporters nationwide, to request that the FDA authorize generic drug manufacturers to revise generic drug labeling through the changes-being-effected (CBE) and prior-approval-supplement (PAS) procedures. As discussed below, since enactment of the Hatch-Waxman Amendments in 1984, the prescription-drug market has been transformed, as sales of generic drugs have skyrocketed and now constitute the majority of all prescriptions filled. Yet despite considerable changes in the market, FDA regulation of generic labeling has remained substantially unchanged. The regulatory revisions requested here would bring post-market regulation in line with the realities of the pharmaceutical market and help to ensure that drug labeling provides adequate warnings to patients based on information that comes to light after the drug is approved for marketing.

I. ACTIONS REQUESTED

Public Citizen requests that, through notice and comment rulemaking, the FDA amend 21 C.F.R. § 314.70(a) to specify that 21 C.F.R. § 314.70(b) and (c) apply to abbreviated new drug application (ANDA) holders. This amendment would authorize an ANDA holder to change that drug's approved label by filing a supplement through the CBE and PAS procedures. The amendment might also make exceptions to reflect situations in which the agency believes that particular ANDA holders lack an adequate basis to make labeling changes, such as, perhaps, during the first few months after the first ANDA holder enters the market or for an ANDA holder that sells very few prescriptions of a drug (for example, under 1,000 prescriptions per year).

Public Citizen also requests that the FDA amend regulations that permit ANDA approval to be withdrawn if a generic drug's approved labeling differs from that of the

reference listed drug (RLD), *see, e.g.*, 21 C.F.R. § 314.150(b)(10), to specify that this regulation does not apply to ANDA holders permitted to supplement labeling through CBE or PAS procedures. Finally, Public Citizen requests that the FDA clarify that *all* ANDA holders are required to report safety concerns to the FDA as soon as they become aware of a clinically significant hazard. Part III, below, contains a more detailed statement of the action requested and proposes language for amended regulations.

II. STATEMENT OF GROUNDS

A. MANUFACTURERS OF GENERIC DRUGS PRODUCE A MAJORITY OF THE PRESCRIPTION DRUGS SOLD IN THE UNITED STATES.

Following passage of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585, commonly referred to as the Hatch-Waxman Amendments, sales of generic drugs have grown dramatically, fundamentally reshaping the pharmaceutical market. The increased availability of generic drugs has made many prescription drugs more affordable for patients. Gen. Pharm. Ass'n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009* (2010). In 1983, only 35 percent of top-selling drugs with expired patents had generic equivalents; by 1998, nearly all did. Congressional Budget Office, *How Increased Competition From Generic Drugs Has Affected Prices and Return in the Pharmaceutical Industry*, at xii (1998). And when generics compete, they typically capture a significant part of market share and profit. *See* Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* 16-17 (2006). As of 2010, 90 percent of prescriptions for drugs with generic versions were filled with a generic rather than the brand-name, HHS, *ASPE Issue Brief: Expanding the Use of Generic Drugs* 3-4 (2010), a development spurred by state laws authorizing pharmacists to substitute generic drugs when filling prescriptions. *See* Thomas P. Christensen et al., *Drug Product Selection: Legal Issues*, 41 J. Am. Pharm. Ass'n 868 (2001). Some states have gone further and now mandate generic substitution where available. William H. Shrank et al., *State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid*, 29 Health Affairs 1383 (July 2010). From 2009 to 2010 alone, generic prescriptions' share increased by 4 percent to reach 78 percent of all U.S. prescriptions. IMS Institute for Healthcare Informatics, *The Use of Medicines in the United States: Review of 2010* 11, 15, 22 (April 2011) (IMS Report). In 2010, generics captured more than 80 percent of the market within six months of expiration of the brand-name's patent (as compared to 55 percent in 2006). *Id.* at 21.

Generic manufacturers' market growth has been accompanied by an expansion in their profit margins and research capabilities. Contrary to popular belief, obtaining FDA approval for a generic drug remains a substantial undertaking that requires a significant investment of scientific expertise and research funding. *See* David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics*, 87 Rev. of Econ. & Stats. 37, 38 (2005) ("In the vast majority of cases, the initial ANDA application is found deficient, requiring the applicant to conduct additional tests or submit additional material."). Generic manufacturers accordingly spend millions of dollars annually on research and development. *See, e.g.*, Teva Pharm. Indus. Ltd, Annual report 2009, at 48 (2010),

available at <http://www.tevapharm.com/pdf/teva20F2009.pdf> (noting that in 2009 Teva Pharmaceuticals spent approximately 63 percent of a total \$802 million in R&D expenses on generic R&D). In some cases, brand-name and generic R&D overlap. *See, e.g., id.* at 11. For example, two of the top five generic manufacturers are also divisions of major brand-name manufacturers with well-known new drug research programs (Sandoz and Greenstone, which are divisions respectively of Novartis and Pfizer). *See* Alaric Dearment, *Countdown to 2011: A Big Year for Generics*, Drug Store News, Nov. 14 2010, available at <http://www.drugstorenews.com/article/countdown-2011-big-year-generics>.

Successful competition from generics has led some brand-name manufacturers to cease production of out-of-patent drugs. As a group of health policy experts and professors of pharmaceutical regulation recently stated: “Our own analysis of FDA data indicates that out of 4,653 approved drugs with distinct ingredients, delivery routes, and strengths, more than half—2,438—are available in generic form. Of those, 1,062 are available *solely* in generic form; the only available versions of the drug received ANDA approval.” Brief for Marc T. Law et al. as Amici Curiae Supporting Resp’ts, *Pliva v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09–993, 09–1039, 09–1501) at 18 (Brief of Pharm. Reg. Experts). Another study reported that, in 2009, 32 percent of 4,318 unique drug molecules were sold solely as generics. Generic Pharm. Ass’n, *Savings Achieved Through the Use of Generic Pharmaceuticals 2000-2009*, at 7 (2010).

B. POST-APPROVAL MONITORING IS ESSENTIAL TO THE SAFETY OF DRUGS AND IS A SHARED RESPONSIBILITY OF THE FDA AND MANUFACTURERS.

The importance of post-approval monitoring for drug safety is well-recognized. As two scholars recently explained:

Even though the evaluation of new drugs and devices is technically rigorous, the current approach of basing drug approval decisions on clinical trials of efficacy that include relatively small numbers of patients virtually guarantees that the full risks and complete safety profile of these drugs will not be identified at the time of approval. Rather, the full safety profile and effectiveness only manifest as each drug is used in the wider population of patients who are less carefully selected than participants in clinical trials.

Catherine D. DeAngelis & Phil B. Fontanarosa, *Prescription Drugs, Products Liability, and Preemption of Tort Litigation*, 300 J. Am. Med. Ass’n 1939, 1939 (2008). The limitations in pre-approval testing are especially salient when a drug’s risks are relatively rare or have long latency periods—forms of risk that the FDA approval process is not designed to uncover. David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA’s Efforts to Preempt Failure-to-Warn Claims*, 96 Geo. L.J. 461, 483 (2008). Examples of drugs whose substantial risks were only discovered post-approval abound in the medical literature. *See* Brief of the Am. Med. Ass’n et al. as Amici Curiae Supporting Resp’ts *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09–993, 09–1039, 09–

1501), at 12-17 (discussing as examples fenfluramine, propoxyphene, ibuprofen, terbutaline sulfate, and metoclopramide); Brief of Pharm. Reg. Experts 29-30 (discussing Neurontin, metoclopramide, and Darvon). In particular, off-label uses, some of which become popular after a generic option is on the market, may lead to unforeseen side effects. *See* Brief of Pharm. Reg. Experts 30-31 (discussing example of trazodone).

Moreover, some generic drugs may be associated with adverse events that do not occur with the name-brand drug. *See* Brief of Pharm. Reg. Experts 30-31 (discussing Budeprion XL as an example of a generic drug with side effects not associated with Wellbutrin XL, its brand-name counterpart). Under current regulations, the FDA has sole responsibility for updating generic labeling to reflect such hazards, as the generic manufacturer may not revise labeling on its own to reflect newly discovered hazards.

As the Supreme Court recognized in *Wyeth v. Levine*, “[t]he FDA has limited resources to monitor the 11,000 drugs on the market, and manufacturers have superior access to information about their drugs, especially in the postmarketing phase as new risks emerge.” 129 S. Ct. 1187, 1202 (2009) (footnote omitted). It has therefore been “a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times . . . [and] ensuring that its warnings remain adequate as long as the drug is on the market.” *Id.* at 1197-98. The need for manufacturers to play a significant role is heightened by funding and staff shortages at the FDA that have prompted the Government Accountability Office (GAO) to repeatedly express concern about post-approval drug safety monitoring. *See, e.g.,* GAO, *High-Risk Series: An Update* 116-17 (Feb. 2011) (“FDA staff have expressed concern about their ability to meet a growing postmarket workload, with some maintaining that their premarket responsibilities are considered a higher priority.”); GAO, *Drug Safety: FDA Has Begun Efforts to Enhance Postmarket Safety, but Additional Actions Are Needed* (Nov. 2009); GAO, *Drug Safety: Improvement Needed in FDA’s Postmarket Decisionmaking and Oversight Processes* (Mar. 2006); *see also* Kessler & Vladeck, *A Critical Examination*, 96 *Geo. L.J.* at 485 (noting that “[r]esource constraints have been especially acute with the agency’s post-marketing surveillance efforts” and that two-thirds of FDA doctors and scientists “worry that the FDA is not adequately monitoring the safety of drugs once they are on the market”).

All manufacturers—brand-name and generic—must therefore comply with an extensive set of regulations designed to ensure the post-approval safety of their drugs. Of particular relevance, manufacturers “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, post-marketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.” 21 C.F.R. § 314.80(b) (rendered applicable to ANDA holders by 21 C.F.R. § 98(a)). Any report of a “serious and unexpected” drug experience, whether foreign or domestic, must be reported to the FDA within 15 days and must be promptly investigated by the manufacturer. 21 C.F.R. § 314.80(c)(1)(i-ii). Most other adverse event reports must be submitted quarterly for three years after the application is approved and annually

thereafter. 21 C.F.R. § 314.80(c)(2)(i). These periodic reports must include “a history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated).” 21 C.F.R. § 314.80(c)(2)(ii). Generic manufacturers, like their brand-name counterparts, must therefore participate actively in ongoing pharmacovigilance to comply with FDA regulations.

To ensure that labeling is kept up to date as information accumulates, FDA regulations require that “the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established.” 21 C.F.R. § 201.57(c)(6)(i) (implementing 21 U.S.C. § 352(f)(2), which provides that a drug lacking “adequate warnings” is misbranded).

Brand-name manufacturers may seek to change their approved labels by filing a supplemental application. 21 C.F.R. § 314.70. A supplemental application must satisfy all regulatory requirements that apply to original applications. *See* 21 C.F.R. § 314.3(b). Although some label changes require prior FDA approval—obtained through a PAS, 21 C.F.R. § 314.70(b)—other changes are brought to FDA’s attention “at the time the applicant makes [the] change” through a CBE supplement. 21 C.F.R. § 314.70(c). CBE supplements are authorized for, among other things, “[c]hanges in the labeling to reflect newly acquired information . . . [t]o 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.” 21 C.F.R. § 314.70(c)(6)(iii)(A).

Although by their terms the PAS and CBE regulations would seem to apply to both generic and brand-name manufacturers, *see also* 21 C.F.R. § 314.97 (requiring ANDA holders to comply with “requirements [applicable to NDA holders] regarding the submission of supplemental applications”), the FDA has stated that the PAS and CBE processes are not available to generic manufacturers. Instead, the FDA has explained that under current regulations, ANDA holders must generally abide by a “sameness” requirement to keep their label “the same as the labeling of the reference listed drug [RLD].” 21 C.F.R. § 314.94(a)(8)(iii); *see also* 21 C.F.R. § 314.105(c). At the same time, recognizing that there may be reasons to deviate from the sameness requirement, FDA regulations make exceptions for certain types of information. *See id.* § 314.94(a)(8)(iv).¹

The FDA recently addressed the operation of its post-approval labeling regulations in its amicus brief in *PLIVA v. Mensing*. In that case, the Supreme Court considered whether the restrictions imposed by federal law on the ability of generic drug manufacturers to alter labeling preempts state common-law claims against a generic manufacturer based on failure to warn of hazards associated with its product. Looking to the regulatory limitations on ANDA holders’ ability to revise labeling, the Court concluded that “it was

¹ For a fuller discussion of brand-name and generic drug labeling, *see, e.g.*, Brief for the United States as Amicus Curiae Supporting Resp’ts, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011) (Nos. 09–993, 09–1039, 09–1501) (U.S. Brief).

impossible for the Manufacturers to comply with both their state-law duty to change the label and their federal law duty to keep the label the same.” *PLIVA*, 131 S. Ct. at 2578.

Specifically, the Court deferred to the FDA’s position that generic manufacturers cannot invoke CBE or PAS procedures to change labeling because doing so would violate the requirement under 21 C.F.R. § 314.94(a)(8)(iii) that generic and name-brand labeling be the same. *PLIVA*, 131 S. Ct. 2575; *see* U.S. Brief 16 (“FDA has consistently taken the position that an ANDA holder may not unilaterally change its approved labeling”); *id.* at 17 (“The PAS process also was not available to petitioners to make the labeling change respondents envision.”). The FDA’s position was based in part on a 1992 Federal Register notice in which the agency had stated that “an ANDA holder wishing to add a warning should furnish adequate supporting information to FDA, which would then determine whether the labeling for all drugs should be modified.” U.S. Brief 17. The Court also deferred to the FDA’s view that generic manufacturers cannot unilaterally send a “Dear Doctor” letter. *PLIVA*, 131 S. Ct. 2576

C. GENERIC MANUFACTURERS’ LACK OF RESPONSIBILITY FOR ENSURING THE POST-APPROVAL ADEQUACY OF PRODUCT LABELING THREATENS PATIENT SAFETY.

The FDA’s position on the inapplicability of 21 C.F.R. § 314.70 to ANDA holders, and the Supreme Court’s recent decision in *PLIVA*, which turns on the limitations of the regulatory scheme, threaten the safety of prescription drugs, and accordingly, pose unnecessary risks to patients.

First, as explained above, generics compete effectively with out-of-patent brand-name drugs, making prescription drugs more affordable. Yet while their market shares have increased, the regulatory system has not adjusted to compel generic manufacturers to shoulder responsibility commensurate with their status as major market players. At the same time, the rise of generics has weakened incentives for brand-name manufacturers to remain actively engaged in the market for their products after losing patent protection.

Under the product liability law of many states, the brand-name company cannot be held liable drug for harm caused by inadequate labeling where the injured patient took a generic form of the drug. Jim Beck & Mark Hermann, *Scorecard: Non-Manufacturer, Brand Name Defendants in Generic Drug Cases*, Drug and Device Law Blog (Nov. 12 2009), *available at* <http://druganddevicelaw.blogspot.com/2009/11/scorecard-non-manufacturer-name-brand.html> (collecting cases). When more than 75 percent of all prescriptions are filled by generic versions, this legal reality further diminishes the name-brand manufacturer’s incentive to be vigilant and to take the time and expense to submit a CBE or PAS.

These developments collectively give rise to a safety problem: As generic market share increases, the brand-name manufacturer loses incentive to invest resources in post-approval safety monitoring, while generic manufacturers face no concomitant increase in incentive and have no authority to update labeling. Given that the FDA cannot monitor

all post-approval data by itself, drug safety is threatened when the regulatory and common-law incentives designed to motivate manufacturer diligence weaken with shifting control of market share.

The current system is also illogical. As noted earlier, the FDA has recently interpreted the “sameness” requirement under 21 C.F.R. § 314.94(a)(8)(iii) to preclude generic-initiated changes to the label through a CBE or PAS supplement. As a result, current regulations prevent generic manufacturers from providing physicians and patients with updated safety information in light of newly discovered risks. The generic manufacturers are only able to report concerns to the FDA. Yet, as discussed above, those manufacturers frequently control most of a drug’s market share and make the most profit from that drug. Even more important, because of their market share, they are likely the main recipients of adverse event reports, may be best informed regarding risks unique to off-label use, and already must compile information about risks on a periodic basis under post-approval reporting regulations. Drug safety would benefit if generic manufacturers who already have access to much of the relevant information were able to use CBE and PAS procedures to revise labeling. Once a manufacturer has achieved a certain market share, it should be given the tools to share responsibilities for drug safety and labeling.

Regulatory changes to correct this gap would not impose an obligation beyond the capacity of generic manufacturers. It is our understanding that, under current regulations, a generic manufacturer is designated by the FDA to maintain the label of a drug when the name-brand manufacturer of that drug withdraws from the market. This procedure manifests the FDA’s confidence in the ability of generic manufacturers to perform ongoing pharmacovigilance duties—which makes sense, given their substantial scientific and financial resources, as well as the effort they must already invest to comply with post-approval safety regulations.

Second, as discussed above, in *PLIVA*, the Supreme Court held that because generic manufacturers cannot satisfy state common-law duties to amend the drug’s label while complying with FDA regulations, those state-law duties were preempted.

The dissent in *PLIVA* noted (and the majority did not disagree) that the Court’s holding produces “absurd consequences.” 131 S. Ct. at 2592. First, it threatens drug safety by creating a “gap in the parallel federal-state regulatory scheme.” *Id.*; see also *Wyeth*, 129 S. Ct. at 1203 (“[T]he FDA long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.”). Second, it denies compensation to consumers injured by drugs with inadequate warnings on the arbitrary basis of whether their prescriptions were filled with a brand-name or generic. In this way, the holding—and the regulatory scheme on which it is based—deviates from the “sameness” principle central to Hatch-Waxman by distinguishing generics in a crucial respect: “Consumers of brand-name drugs can sue manufacturers for inadequate warnings; consumers of generic drugs cannot.” *PLIVA*, 131 S. Ct. at 2593 (Sotomayor, J., dissenting). The FDA expressed similar concerns in its amicus brief to the Court, noting that generic manufacturers “argue that they enjoy a free pass accorded to virtually no other manufacturer regarding product labeling—in the field

of drugs or otherwise.” U.S. Brief 26. In addition, the outcome is in tension with generic substitution laws, as they encourage or even require that prescriptions be filled with generic drugs when possible, but patients’ inability to hold generic manufacturers accountable for inadequate labeling (whether the inadequacy is specific to a hazard associated with that generic or applies to the drug more generally) provides incentive for patients to request the brand-name drug instead of the generic. This outcome is also directly contrary to the objective of Hatch-Waxman.

The virtues of state common law as an adjunct to FDA drug safety regulations are well-established. As Justice Stevens explained in *Wyeth*:

State tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly. They also serve a distinct compensatory function that may motivate injured persons to come forward with information. Failure-to-warn actions, in particular, lend force to the FDCA’s premise that manufacturers, not the FDA, bear primary responsibility for their drug labeling at all times.

129 S. Ct. at 1202. State-law remedies thus “further consumer protection by motivating manufacturers to produce safe and effective drugs and to give adequate warnings.” *Id.* at 1200; *see also* Margaret Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 11 (1997) (article by then-FDA Chief Counsel, stating that “[e]ven the most thorough regulation of a product such as a critical medical device may fail to identify potential problems presented by the product. Regulation cannot protect against all possible injuries that might result from use of a device over time. Preemption of all such claims would result in the loss of a significant layer of consumer protection . . .”). Post-*PLIVA*, preemption of common-law claims against generic manufactures will strip a vast portion of the market of these safeguards.

Generic manufacturers’ immunity from state common-law suits is contingent on the Court’s finding that the manufacturers’ cannot change their products’ labeling under current FDA regulations, even if they learn about new risks. According to the Court, the inability to change labeling renders it impossible for generic manufacturers to comply with both federal and state obligations, giving rise to implied preemption of state law. Amending FDA regulations to permit generic manufactures to make use of PAS and CBE procedures in response to new risk information would undo this impossibility. In that event, common law could once again complement the FDA’s mandate to monitor drug safety across the full range of drugs, rather than just the decreasing portion occupied by brand-name drugs. The action requested in this petition would not only eliminate the absurd inconsistency in common-law protections based on the happenstance of whether the patient ingested the generic or brand-name form of the drug, it would also restore marketplace equality, as both types of manufacturers would face the same potential liability for failures to adequately warn of hazards associated with their products.

III. DETAILED DESCRIPTION OF REQUESTED ACTION

“[T]he FDA has no ‘formal regulation’ establishing generic drug manufacturers’ duty to initiate a label change, nor does it have any regulation setting out that label change process.” *PLIVA*, 131 S. Ct. at 2582 n.9 (quoting U.S. Brief 20-21). Filling this regulatory gap will help to ensure that drug labeling is updated to provide warnings based on new information to protect patient safety. Accordingly, FDA regulations should be revised to allow ANDA holders to use the PAS and CBE procedures. The FDA should also clarify the view, first articulated in its 1992 regulations implementing the Hatch-Waxman Amendments, *see* 57 Fed. Reg. 17950, 17961 (1992), that all ANDA holders have a duty to report safety concerns to the FDA.

Our proposal would authorize all ANDA holders to use the CBE and PAS procedures. As mentioned above (at p.2), within six months of patent expiration, the brand-name manufacturer’s market share drops to twenty percent or less. At that point, to continue to rely solely on a single manufacturer serving a minority of the market for a particular drug is neither required by Hatch-Waxman nor the best way to protect patients. We recognize, however, that the FDA may want to carve out exceptions. For example, the agency may want to consider an exception for the first few months that the first ANDA holder of a particular drug enters the market, or for an ANDA holder that sells few prescriptions of a particular drug and is not in a position to identify previously unknown risks or labeling deficiencies based on real-world use. Any exceptions could be added to our proposed 21 C.F.R. § 314.70(a)(7). At the same time, for all generic manufacturers, we urge the FDA strongly to reiterate the manufacturers’ obligation to inform the FDA whenever the manufacturer becomes aware of information suggesting an association between the product and a hazard not adequately disclosed on the labeling.

Specifically, we suggest the following revisions (current regulations in standard type, additions in italics):

21 C.F.R. § 314.70(a)

(7) The supplement procedures specified in paragraphs (b) and (c) of this section may be employed by an ANDA holder.

21 C.F.R. § 314.150(b)(10)

(b) FDA may notify the applicant, and, if appropriate, all other persons who manufacture or distribute identical, related, or similar drug products as defined in § 310.6, and for a new drug afford an opportunity for a hearing on a proposal to withdraw approval of the application or abbreviated new drug application under section 505(e) of the act and under the procedure in § 314.200, if the agency finds:

(10) That the labeling for the drug product that is the subject of the abbreviated new drug application is no longer consistent with that for the listed drug referred to in the abbreviated new drug application, except for differences approved in the abbreviated new drug application or those differences resulting from:

- (i) A patent on the listed drug issued after approval of the abbreviated new drug application; or
- (ii) Exclusivity accorded to the listed drug after approval of the abbreviated new drug application that do not render the drug product less safe or effective than the listed drug for any remaining, nonprotected condition(s) of use.
- (iii) *Changes in the ANDA holder's drug product labeling made pursuant to the "prior approval supplement" or "changes being effected" supplement procedures, as applicable to ANDA holders under 21 C.F.R. § 314.70(a)(7).*

21 C.F.R. § 201.57(c)(6)(i)(A)

(i) General. This section must describe clinically significant adverse reactions (including any that are potentially fatal, are serious even if infrequent, or can be prevented or mitigated through appropriate use of the drug), other potential safety hazards (including those that are expected for the pharmacological class or those resulting from drug/drug interactions), limitations in use imposed by them (e.g., avoiding certain concomitant therapy), and steps that should be taken if they occur (e.g., dosage modification). The frequency of all clinically significant adverse reactions and the approximate mortality and morbidity rates for patients experiencing the reaction, if known and necessary for the safe and effective use of the drug, must be expressed as provided under paragraph (c)(7) of this section. In accordance with §§ 314.70 and 601.12 of this chapter, the labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug; a causal relationship need not have been definitely established. A specific warning relating to a use not provided for under the "Indications and Usage" section may be required by FDA in accordance with sections 201(n) and 502(a) of the act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard.

- A. *NDA holders and ANDA holders authorized under 21 C.F.R. § 314.70(a)(7) to use the procedures set forth in 21 C.F.R. § 314.70 (b) and (c) may satisfy this provision's requirement that labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug, even if a causal relationship has not been definitely established, using the procedures set forth in 21 C.F.R. § 314.70 (b) and (c).*
- B. *Whether or not authorized to effect labeling changes under 21 C.F.R. § 314.70(a)(7), an ANDA holder that becomes aware of reasonable evidence of a causal association of a drug with a significant hazard (even if a causal*

relationship has not been definitely established) must promptly inform and provide such evidence to the FDA.²

IV. ENVIRONMENTAL IMPACT

The actions requested in this petition will have no significant effect on the human environment.

V. CERTIFICATION

To the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies and includes representative data and information known to the petitioner that are unfavorable to the petition.



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² The amendment to 21 C.F.R. § 201.57(c)(6)(i)(A) would be necessary only if the FDA makes exceptions to the general rule allowing ANDA holders to use the CBE and PAS procedures.