Congress of the United States
Washington, DC 20510

March 5, 2014

Doctor Margaret Hamburg
Commissioner, Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

Re: Proposed Rule for Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products

Dear Commissioner Hamburg:

We write in strong support of the Food and Drug Administration (FDA) Proposed Rule, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products*,[1] which would enable manufacturers of generic drugs to update labeling on their products to reflect new patient safety information. The Proposed Rule is critically important to ensure that the public is informed as soon as possible when new safety information becomes available, and to ensure that labeling for a prescription drug remains up-to-date even when the branded drug is no longer being marketed or has not undergone a labeling update to reflect newly discovered risks.

The "Changes Being Effected" (CBE) process that the Proposed Rule would make available to holders of an approved Abbreviated New Drug Application ("ANDA" holders, or generic drug manufacturers) serves an important public safety function. It ensures that patients and doctors are made aware of new safety information "at the earliest possible time."[2] The CBE process enables brand drug manufacturers to strengthen warnings for their products, provide new patient safety information, and make certain other labeling changes with concurrent notice to FDA. This mechanism has provided an important tool for timely communication of safety information to patients and physicians. We agree with FDA that it is in the best interests of patients to ensure that the CBE process may also be used by manufacturers of generic drugs.[3]

Empowering a drug manufacturer to update certain safety information *while* FDA reviews the change, instead of requiring prior FDA approval, will allow generic drug manufacturers to communicate safety information in a timely way.[4] Often, risks associated with a drug do not become known until after a drug has been on the market for

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[1] Docket No. FDA-2013-N-0500; 78 Fed. Reg. 67985 (proposed Nov. 13, 2013).
[2] FDA, Supplemental New Drug Applications, 30 Fed. Reg. 993 (Jan. 30, 1965) (creation of "supplemental new-drug application" process that permitted labeling changes prior to receipt of approval by FDA).
[3] The Proposed Rule would also make clear that generic drug manufacturers may send a "Dear Health Care Provider" letter to physicians regarding a labeling change. *See* 78 Fed. Reg. at 67989.
[4] FDA, New Drug and Antibiotic Regulations, 47 Fed. Reg. 46622, 46634-35 (Oct 19, 1982), 50 Fed. Reg. 7452, 7499 (Feb. 22, 1985) (clarifying Changes Being Effected process).

a number of years, including after generic drugs have entered the market and sales of the branded drug have declined.[5] As the Supreme Court has noted, 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 post-marketing phase as new risks emerge."[6] The CBE process accommodates the important need for safety monitoring after a product enters the market while providing an appropriate measure of FDA review.

We support FDA's conclusion that changes in market circumstances justify regulatory action to ensure that generic drug manufacturers can use the CBE process to make timely updates to their products' safety labeling information. Thanks to important developments in the law and market practices, approximately 80 percent of all prescriptions are now filled by generic drugs.[7] This welcome change has made medicines more affordable and available—objectives we have long championed. However, it also warrants a renewed consideration of generic manufacturers' labeling responsibilities to ensure their products remain safe and are used safely.[8]

Following introduction of a generic drug onto the market, the market share of its brand-name equivalent often drops substantially: among drugs for which a generic version is available, approximately 94 percent are dispensed in a generic form.[9] In some cases, the branded drug exits the market altogether after generic entry, leaving only

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[5] Public Citizen, GENERIC DRUG LABELING: A REPORT ON SERIOUS WARNINGS ADDED TO APPROVED DRUGS AND ON GENERIC DRUGS MARKETED WITHOUT A BRAND-NAME EQUIVALENT (2013), *available at* http://www.citizen.org/hrg2138 (identifying 53 drugs for which a black-box warning calling attention to serious or life-threatening risks was added *after* generic market entry, from Jan. 2008-March 2013); *see also* Catherine D. DeAngelis & Phil B. Fontanarosa, *Prescription Drugs, Products Liability, and Preemption of Tort Litigation*, 300 J. AM. MED. ASS'N 1939 (2008) (concluding that the safety profile of a drug may change considerably in the 10 years following its initial approval, due to the data received from a wider patient population); Karen E. Lasser, et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medicines*, 287 J. AM. MED. ASS'N 2215, 2218 (2002) (finding that half of newly-discovered serious adverse reactions were detected *after* a drug had been on the market for seven or more years).

[6] *Wyeth v. Levine*, 555 U.S. 555, 578 (2009).

[7] Generic Pharmaceutical Ass'n, GENERIC DRUG SAVINGS IN THE U.S. at 2 (2012), *available at* http://www.gphaonline.org/media/cms/IMSStudyAug2012WEB.pdf; IBIS World Industry Report, GENERIC PHARMACEUTICAL MANUFACTURING IN THE U.S. (2013) at 7 ("generic pharmaceuticals now account for more than 80.0% of dispensed prescriptions").

[8] As discussed below, generic manufacturers are already required by statute to maintain accurate labeling information and to engage in ongoing pharmacovigilence. 21 U.S.C. § 331(a)-(b), (k) (2006). Existing regulations require generic manufacturers to conduct post-market surveillance and report adverse events to FDA, accompanied by recommendations for further action. *See* 21 C.F.R § 314.98. The Proposed Rule builds on these existing obligations by permitting generic manufacturers to update certain labeling information at the *same time* FDA reviews the changes, a process for timely updating of information that is now available only to branded drugs. 78 Fed. Reg. at 67995.

[9] Generic Pharmaceutical Ass'n, GENERIC DRUG SAVINGS IN THE U.S. at 3; see also *Protecting Consumer Access to Generic Drugs Act of 2009: Hearing on H.R. 1706 Before the H. Subcomm. on Commerce, Trade and Consumer Protection*, 111th Cong. at 204 (2009) (statement of Diane Bieri, Exec. VP and Gen. Counsel, Pharm. Res. & Mfrs. of Am.) (noting that in 2008, generic drugs typically attained between 86 to 97 percent of the market share within the first month of entry).

generic products on the market.[10] In such instances, generic manufacturers will have the best knowledge of adverse events; indeed, they may be the *only* manufacturers left in the market to monitor a product and ensure its labeling is up-to-date. We agree with FDA's conclusion that this factor weighs heavily in favor of allowing generic drug manufacturers to update their labeling information in the same manner available to brand-name manufacturers, to account for adverse event reports that they receive.

Current rules that preclude generic drug manufacturers from updating their safety information through the CBE process have a detrimental impact on consumers—and, specifically, on our constituents. First, labeling that does not reflect current knowledge about safety risks poses a threat to consumers of both branded and generic drugs alike. Second, in the 2011 case *PLIVA v. Mensing*, the United States Supreme Court held that generic manufacturers cannot be held accountable if a patient is injured due to inadequate information on a product label, because current FDA regulations preclude generic manufacturers from updating their patient safety information. As a result of that case and its interpretation of FDA regulations, consumers who are injured by the generic version of a prescription drug have been foreclosed from seeking any remedy for inadequate labeling, even though consumers who take the brand-name version of the drug *may* seek recourse for their injury.[11] Generics consumers in our states and across the country have been adversely affected as a result.[12]

This disparate outcome for consumers who take generic and brand name drugs is directly counter to the intent of the Hatch-Waxman Act[13] and to generic substitution laws that have been implemented across the country.[14] Physicians have cautioned that inconsistent liability rules for a patient injured by a generic instead of brand-name drug create "an ethical dilemma" for prescribing doctors.[15] As others have noted, "for generics to succeed, they must have equal value to branded drugs. In economic terms, they must

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[10] Public Citizen, GENERIC DRUG LABELING, *supra* n. 5, at 11 (identifying 434 approved drugs for which no brand-name product remains on the market); Congressional Budget Office Report, EFFECTS OF USING GENERIC DRUGS ON MEDICARE'S PRESCRIPTION DRUG SPENDING (2010) at 8 (citing "approximately 100 million prescriptions [in 2007] filled with a generic drug for which there is no alternative brand available because the brand's manufacturer exited the market.")

[11] A majority of courts have held that generic consumers barred from suing the generic manufacturer because of *Mensing* also have no cause of action against the brand-name manufacturer. *See, e.g.*, *Smith v. Wyeth,* 657 F.3d 420 (6th Cir. 2011); *Demahy v. Schwarz Pharma, Inc.*, 702 F.3d 177 (5th Cir. 2012).

[12] For representative patient stories, *see* Alliance for Justice, *Unequal Justice: Pliva v. Mensing, available at* http://www.afj.org/multimedia/first-monday-films/unequal-justice-pliva-v-mensing.

[13] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 5585; *see Drug Price Competition and Patent Term Restoration Act of 1984: Hearing on S. 2748 Before the S. Comm. on Labor & Human Res.*, 98th Cong. (1984).

[14] Department of Health & Human Services, EXPANDING THE USE OF GENERIC DRUGS (2010), app. A, *available at* http://aspe.hhs.gov/sp/reports/2010/GenericDrugs/ib.shtml (listing generic substitution laws). Fifteen states, including several of the states we represent, require a pharmacist to substitute a generic drug unless a physician directs no substitution should take place.

[15] Brief of the Am. Med. Ass'n et al. as Amici Curiae in Support of Respondents at 15-16, *PLIVA v. Mensing*, 131 S. Ct. 2567 (2011), 2011 WL 794118 at *29 ("Divergent liability rules for brand name and generic drugs pose an ethical dilemma for physicians.")

be perfect substitutes, and, in safety terms, this requires a duty to disclose risks equal to that of its branded drug. A critical component of the value equation for any product is a consumer's recourse in the event the product is defective."[16]

Some have expressed concern that allowing ANDA holders to use the CBE process will impose undue costs on generic manufacturers and, therefore, patients. This concern appears unfounded. To begin with, ANDA holders are already obligated to monitor the safety of their products and recommend safety labeling improvements under current law.[17] Existing regulations already require generic manufacturers to conduct post-market surveillance, to report adverse events to FDA, and to submit reports to FDA summarizing information that might affect the labeling of a drug.[18] The Proposed Rule simply builds on those existing reporting obligations to permit generic manufacturers to use the CBE process to update their labeling information.

As FDA has found, however, the inability of a generic drug manufacturer to improve labeling information—and to be held accountable to patients if it fails to do so—"alters the incentives for generic drug manufacturers to comply with current requirements to conduct robust post-marketing surveillance, evaluation, and reporting, and to ensure that the labeling for their drugs is accurate and up-to-date."[19] State tort law serves an important role in ensuring that manufacturers comply with their obligation to conduct post-marketing surveillance for their products. As the Supreme Court has noted, FDA has "long maintained that state law offers an additional, and important, layer of consumer protection that complements FDA regulation."[20] State laws motivate manufacturers to give adequate warnings, and the potential for tort liability provides an important check where FDA's enforcement resources for supervising post-market surveillance are stretched thin. In addition, and most importantly, better warnings reduce injury. As a result, better warnings reduce, not increase, the number of patients needing compensation for injury.

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[16] Stacey B. Lee, PLIVA v. Mensing: *Generic Consumers' Unfortunate Hand*, 12 YALE J. HEALTH POLICY, LAW & ETHICS 209, 241 (2012) (further noting, "Th[e] absence of generic manufacturer oversight may reasonably diminish consumer confidence in the safety and effectiveness of generic drugs.")

[17] *See* 21 U.S.C. § 331(a)-(b), (k) (2006).

[18] *See* 21 C.F.R § 314.98; 21 U.S.C. §355(k).

[19] 78 Fed. Reg. at 67988-89.

[20] *Wyeth v. Levine,* 555 U.S. at 579 (noting also, "state tort suits uncover unknown drug hazards and provide incentives for drug manufacturers to disclose safety risks promptly"). *See also* Brief of the Am. Med. Ass'n et al. as Amici Curiae in Support of Respondents, *Pliva v. Mensing, supra* note 15, at 25 ("The longstanding coexistence of state and federal law and FDA's traditional recognition of state law remedies buttress the conclusion that state law offers an additional, and important, layer of consumer protection that complements FDA regulation.") (internal citations omitted); Lee, 2 YALE J. HEALTH POLICY, LAW & ETHICS at 243 ("The potential damage awards from state failure-to-warn litigation provides drug manufacturers with incentives to quickly provide full and clear information to physicians and FDA that otherwise may not come to light. Without such a mechanism, generic manufacturers may be motivated to act merely in their immediate financial interest, and, subsequently, become less forthcoming in providing safety-related data.")

The Proposed Rule achieves an important public safety goal by restoring these incentives for generic manufacturers to warn consumers of safety risks. Especially in light of resource constraints facing FDA, the potential for tort liability provides an important tool in incentivizing compliance with existing reporting obligations, to the benefit of American consumers.

We understand that some have raised concerns that the policies in the Proposed Rule could result in inconsistent labels between and among branded and generic versions of specific products. As one of us has stated in an amicus brief submitted in *PLIVA v. Mensing*[21] and reiterated in a letter to you last year,[22] it is critical that the principle of sameness in our generic drug system be preserved. The Proposed Rule includes important measures to address this concern, by providing that the ANDA holder shall distribute its revised product labeling "on a temporary basis" while FDA reviews the labeling change (filed as a "CBE Supplement") as described in the Proposed Rule.[23] Notably, the Proposed Rule requires the ANDA holder to submit its labeling change to the relevant brand-name manufacturer for the drug (if one exists) to ensure that the brand-name manufacturer receives up-to-date information and participates in the labeling review. The new labeling information will also be posted to an FDA web page so that it is available to prescribing health care providers and the public. Following FDA's approval of the labeling change, all other ANDA holders for that drug must submit conforming labeling changes within a period of 30 days (unless FDA orders otherwise), to ensure consistency of labeling.[24]

This process strikes an appropriate balance between ensuring that up-to-date safety information is made available as quickly as possible, while promoting consistency in labeling. While some temporary discrepancies in labeling will occur during the period in which the ANDA-holder's CBE Supplement is reviewed, the provisions described above seek to minimize those discrepancies.[25] Notably, similar differences in labeling information *already* occur between the time when a brand name manufacturer submits a CBE Supplement reflecting a labeling change for a specific product, and when the

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[21] Brief for Rep. Henry A. Waxman as Amicus Curiae, *Pliva, Inc. v. Mensing*, 2011 WL 794113, at *1.
[22] Letter from Rep. Waxman, Ranking Member, House of Representatives Committee on Energy & Commerce to Commissioner Hamburg (April 11, 2012), *available at* http://democrats.energycommerce.house.gov/sites/default/files/documents/Hamburg-Generic-Drug-Labeling-2012-4-11.pdf.
[23] 78 Fed. Reg. at 67985, 67989-94.
[24] *Id.* The FDA Amendments Act of 2007 also ensured that FDA may act so that product labeling is promptly amended to accommodate new safety information. Pub. Law 110-85, 121 Stat. 925 (2007).
[25] Although the Hatch-Waxman Act generally requires generic drug labels to have the same labeling as the Registered Listed Drug at the time of approval, the statute permits differences in certain circumstances, including because the drug is produced or distributed by different manufacturers. 21 U.S.C. §355(j)(2)(A)(v) (2013). For example, FDA regulations already permit discrepancies caused by "labeling revisions made to comply with current FDA labeling guidelines or other guidance." 21 C.F.R. § 314.94(a)(8)(iv) (2014).

labeling change receives FDA approval and must be implemented by all ANDA-holders for that drug.[26]

In sum, we agree with FDA's conclusion that "concerns related to temporary differences in labeling between generic drugs and their RLDs are outweighed by the benefit to the public health that would result from all application holders having the ability to independently update drug product labeling to reflect newly acquired information regarding important drug safety issues through CBE-0 labeling supplements."[27] The FDA's general policy of promoting "sameness" for generic and branded drugs is intended "to preclude a basis for lack of confidence in the equivalency of generic versus brand name products."[28] The public safety benefit of enabling generic manufacturers to update their labels, coupled with the process created by the Proposed Rule to ensure conforming changes in equivalent products, advances this goal.

We share a common objective of ensuring that safe, affordable generic drugs are available to all consumers. At the same time, we believe strongly that all drug makers, including generic manufacturers, should be able to take appropriate steps to enhance warning information given to doctors and consumers. In April 2012, several signatories of this letter introduced legislation in the Senate and House of Representatives that would permit manufacturers of generic drugs to update their labeling to provide additional safety information using the CBE process.[29] In 2012 and 2013, we and other members of Congress also wrote to FDA to urge you to address this important issue through regulation.[30] We are pleased that FDA has taken up this issue and developed a proposed rule that promotes the rapid updating of safety labeling information while achieving uniformity across labels in a manner that minimizes burdens on drug manufacturers and physicians.

We applaud FDA's development of this policy. Once finalized, the Proposed Rule will take a significant step towards improving consumer safety information and ensuring equal protection for the millions of Americans who take generic drugs. We urge the agency, after careful and appropriate consideration of all comments, to prioritize release of a final rule.

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[26] *See* FDA, GUIDANCE FOR INDUSTRY: REVISING ANDA LABELING FOLLOWING REVISION OF THE RLD LABELING, at 5 (May 2000), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072891.pdf.

[27] 78 Fed. Reg. at 67995.

[28] Brief for United States as Amicus Curiae Supporting Respondents, *PLIVA, Inc. v. Mensing,* 2011 WL 741927, at *4, citing U.S. Food & Drug Admin., Policy and Procedure Guide 37 (1989).

[29] S.2295, 112th Cong. (2012); H.R. 4384, 112th Cong. (2012).

[30] Letter from Sens. Leahy, Harkin, Franken, and Reps. Van Hollen, Waxman, Braley, and Cartwright to Commissioner Hamburg (June 24, 2013), *available at* http://www.leahy.senate.gov/press/leahy-van-hollen-and-members-of-house-and-senate-join-in-bicameral-effort-urging-the-fda-to-protect-consumers-who-rely-on-generic-prescriptions; Letter from Sens. Leahy, Harkin and Franken to Commissioner Hamburg (May 9, 2012), *available at* http://www.leahy.senate.gov/download/5-9-12-letter-to-fda; Letter from Rep. Waxman to Commissioner Hamburg (April 11, 2012), *available at* http://democrats.energycommerce.house.gov/sites/default/files/documents/Hamburg-Generic-Drug-Labeling-2012-4-11.pdf.

Sincerely,

Senator Patrick J. Leahy
Chairman
Senate Judiciary Committee

Representative Henry Waxman
Ranking Member
House Energy & Commerce Committee

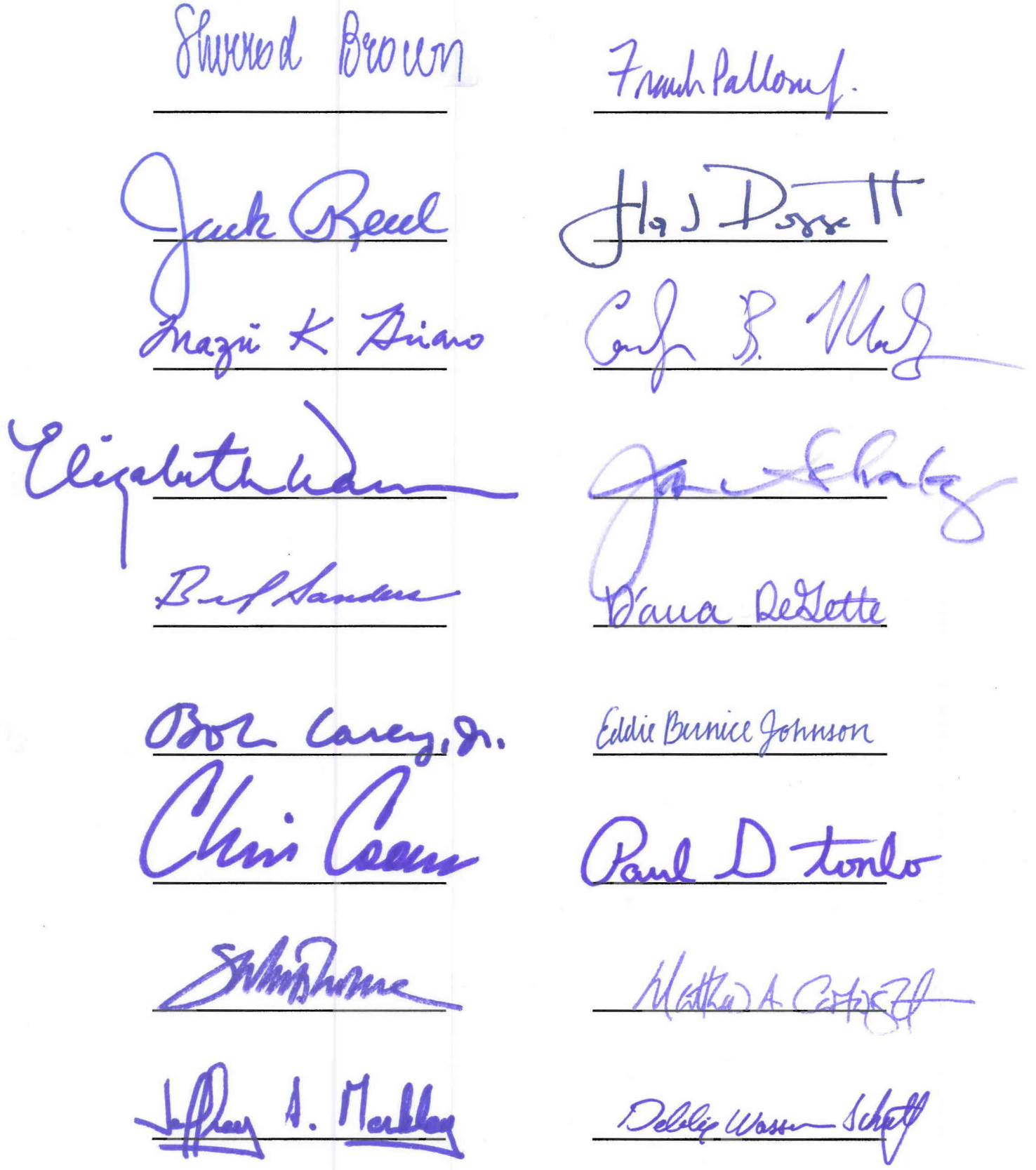
Senator Tom Harkin
Chairman
Senate Health, Education, Labor, & Pensions Committee

Representative John Conyers, Jr.
Ranking Member
House Judiciary Committee

Senator Al Franken

Representative Chris Van Hollen

Representative Bruce Braley



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