EXAMINING CONCERNS REGARDING FDA'S PROPOSED CHANGES TO GENERIC DRUG LABELING

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH

OF THE

COMMITTEE ON ENERGY AND COMMERCE
HOUSE OF REPRESENTATIVES

ONE HUNDRED THIRTEENTH CONGRESS

SECOND SESSION

APRIL 1, 2014

Serial No. 113–132

Printed for the use of the Committee on Energy and Commerce
energycommerce.house.gov

U.S. GOVERNMENT PUBLISHING OFFICE

90–742 WASHINGTON : 2016

For sale by the Superintendent of Documents, U.S. Government Publishing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON ENERGY AND COMMERCE

FRED UPTON, Michigan
Chairman

RALPH M. HALL, Texas
JOE BARTON, Texas
Chairman Emeritus
ED WHITFIELD, Kentucky
JOHN SHIMKUS, Illinois
JOSEPH R. PITTS, Pennsylvania
GREG WALDEN, Oregon
LEE TERRY, Nebraska
MIKE ROGERS, Michigan
TIM MURPHY, Pennsylvania
MICHAEL C. BURGESS, Texas
MARSHA BLACKBURN, Tennessee
Vice Chairman
PHIL GINGREY, Georgia
STEVE SCALISE, Louisiana
ROBERT E. LATTA, Ohio
CATHY MCMORRIS RODGERS, Washington
GREGG HARPER, Mississippi
LEONARD LANCE, New Jersey
BILL CASSIDY, Louisiana
BRETT GUTHRIE, Kentucky
PETE OLSON, Texas
DAVID B. MCKINLEY, West Virginia
CORY GARDNER, Colorado
MIKE POMPEO, Kansas
ADAM KINZINGER, Illinois
H. MORGAN GRIFFITH, Virginia
GUS M. BILIRAKIS, Florida
BILL JOHNSON, Missouri
BILLY LONG, Missouri
RENEE L. ELLMERS, North Carolina

HENRY A. WAXMAN, California
Ranking Member
JOHN D. DINGELL, Michigan
Chairman Emeritus
FRANK PALLONE, JR., New Jersey
BOBBY L. RUSH, Illinois
ANNA G. ESHOO, California
ELIOT L. ENGEL, New York
GENE GREEN, Texas
DIANA DEGETTE, Colorado
LOIS CAPPS, California
MICHAEL F. DOYLE, Pennsylvania
JANICE D. SCHAKOWSKY, Illinois
JIM MATHESON, Utah
G.K. BUTTERFIELD, North Carolina
JOHN BARROW, Georgia
DORIS O. MATSUI, California
DONNA M. CHRISTENSEN, Virgin Islands
KATHY CASTOR, Florida
JOHN P. SARBANES, Maryland
JERRY MCNERNEY, California
BRUCE L. BRALEY, Iowa
PETER WELCH, Vermont
BEN RAY LUJAN, New Mexico
PAUL TONKO, New York
JOHN A. YARMUTH, Kentucky

SUBCOMMITTEE ON HEALTH

JOSEPH R. PITTS, Pennsylvania
Chairman

MICHAEL C. BURGESS, Texas
Vice Chairman
ED WHITFIELD, Kentucky
JOHN SHIMKUS, Illinois
MIKE ROGERS, Michigan
TIM MURPHY, Pennsylvania
MARSHA BLACKBURN, Tennessee
PHIL GINGREY, Georgia
CATHY MCMORRIS RODGERS, Washington
LEONARD LANCE, New Jersey
BILL CASSIDY, Louisiana
BRETT GUTHRIE, Kentucky
H. MORGAN GRIFFITH, Virginia
GUS M. BILIRAKIS, Florida
RENEE L. ELLMERS, North Carolina
JOE BARTON, Texas
FRED UPTON, Michigan (ex officio)

FRANK PALLONE, JR., New Jersey
Ranking Member
JOHN D. DINGELL, Michigan
ELIOT L. ENGEL, New York
LOIS CAPPS, California
JANICE D. SCHAKOWSKY, Illinois
JIM MATHESON, Utah
GENE GREEN, Texas
G.K. BUTTERFIELD, North Carolina
JOHN BARROW, Georgia
DONNA M. CHRISTENSEN, Virgin Islands
KATHY CASTOR, Florida
JOHN P. SARBANES, Maryland
HENRY A. WAXMAN, California (ex officio)

CONTENTS

EXAMINING CONCERNS REGARDING FDA'S PROPOSED CHANGES TO GENERIC DRUG LABELING

TUESDAY, APRIL 1, 2014

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The subcommittee met, pursuant to call, at 3:01 p.m., in room 2322 of the Rayburn House Office Building, Hon. Joseph Pitts (chairman of the subcommittee) presiding.

Members present: Representatives Pitts, Burgess, Shimkus, Gingrey, Lance, Guthrie, Bilirakis, Pallone, Green, Barrow, Christensen, Sarbanes, and Waxman (ex officio).

Also present: Representative Braley.

Staff present: Clay Alspach, Chief Counsel, Health; Noelle Clemente, Press Secretary; Paul Edattel, Professional Staff Member, Health; Sydne Harwick, Legislative Clerk; Robert Horne, Professional Staff Member, Health; Carly McWilliams, Professional Staff Member, Health; Chris Sarley, Policy Coordinator, Environment & Economy; Heidi Stirrup, Health Policy Coordinator; John Stone, Counsel, Health; Tom Wilbur, Digital Media Advisor; Ziky Ababiya, Democratic Staff Assistant; Eric Flamm, Democratic FDA Detailee; Karen Lightfoot, Democratic Communications Director and Senior Policy Advisor; and Karen Nelson, Democratic Deputy Committee Staff Director for Health.

OPENING STATEMENT OF HON. JOSEPH R. PITTS, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF PENNSYLVANIA

Mr. PITTS. The subcommittee will come to order. The chair will recognize himself for an opening statement.

One of the great successes in healthcare in the past 30 years has been the introduction and widespread use of generic drugs, saving patients and taxpayers trillions of dollars. Today, nearly 85 percent of drugs dispensed in the U.S. are generics. This success has been possible because consumers and prescribers have confidence that generic drugs approved by the FDA are the "same" as their brand name counterparts, not only in terms of their chemical composition, but also with respect to their safety and effectiveness.

This principle of "sameness" is the backbone of the 1984 Hatch-Waxman Act, which provided the pathway for generic drugs to come to market. A generic product has the same benefits and risk

as the brand name drug and, therefore, the same labeling is required. Ever since enactment, FDA has logically held that this is an ongoing requirement that extends beyond the date of approval. However, on November 13, 2013, the FDA issued a proposed rule that would allow manufacturers of generic drugs to unilaterally change their safety-related labeling, deviating from the brand. Both FDA's legal and policy rationale for this change is dubious at best.

Currently, a generic can only change its label when the branded drug does so and FDA approves the change. In that case, all generics are then required to adopt the same new labeling in a timely manner. This system does not obviate the need for generics to bring new safety-related information to the agency as soon as possible.

Ostensibly, the proposed change is designed to help speed newly acquired safety information about drugs to the consumer. However, FDA has not explained how this rule would actually improve communication of drug safety information to prescribers and patients other than establishing a Web site on which they will post the various labeling proposals.

The only outcome I see if the rule is enacted is mass confusion. The FDA-approved labeling would essentially become just one in a crowd. The proposed rule undermines the "sameness" requirement in Hatch-Waxman and will result in situations where multiple FDA-approved, therapeutically equivalent products will have different safety-related labeling prior to the FDA determining whether such changes are even necessary or appropriately tailored.

Not only is the proposed rule in direct conflict with the plain language of the statute, but it directly contradicts numerous FDA statements and assertions over the years that consistent drug labeling is necessary if consumers and prescribers are to have confidence that generic drugs are as safe and effective as the reference brand name product.

Finally, FDA has admitted that the proposed changes will open generic manufacturers up to greater liability under state tort lawsuits. The added cost of litigation will also cause generic prices to rise exponentially.

I thank all of our witnesses for being here today to discuss these important issues. I look forward to your testimony, and I yield the remainder of my time to Dr. Burgess.

[The prepared statement of Mr. Pitts follows:]

PREPARED STATEMENT OF HON. JOSEPH R. PITTS

The subcommittee will come to order.

The Chair will recognize himself for an opening statement.

One of the great successes in health care in the past 30 years has been the introduction and widespread use of generic drugs, saving patients and taxpayers trillions of dollars.

Today, nearly 85% of drugs dispensed in the U.S. are generics.

This success has been possible because consumers and prescribers have confidence that generic drugs are approved by the FDA as the "same" as their brand name counterparts-not only in terms of their chemical composition, but also with respect to their safety and effectiveness.

This principle of "sameness" is the backbone of the 1984 Hatch-Waxman Act, which provided the pathway for generic drugs to come to market. A generic product has the same benefits and risks as the brand name drug and, therefore, the same

labeling is required. Ever since enactment, FDA has logically held that this is an ongoing requirement that extends beyond the date of approval.

However, on November 13, 2013, the FDA issued a proposed rule that would allow manufacturers of generic drugs to unilaterally change their safety-related labeling, deviating from the brand. Both FDA's legal and policy rationale for this change is dubious at best.

Currently, a generic can only change its label when the branded drug does so and FDA approves the change. In that case, all generics are then required to adopt the same new labeling in a timely manner. This system does not obviate the need for generics to bring new safety-related information to the agency as soon as possible.

Ostensibly, the proposed change is designed to help speed newly acquired safety information about drugs to the consumer. However, FDA has not explained how this rule would actually improve communication of drug safety information to prescribers and patients other than establishing a Web site on which they will post the various labeling proposals.

The only outcome I see if the rule is enacted is mass confusion. The FDA-approved labeling would essentially become just one in a crowd.

The proposed rule undermines the "sameness" requirement in Hatch-Waxman, and will result in situations where multiple FDA-approved, therapeutically equivalent products will have different safety-related labeling prior to the FDA determining whether such changes are even necessary or appropriately tailored.

Not only is the proposed rule in direct conflict with the plain language of the statute, but it directly contradicts numerous FDA statements and assertions over the years that consistent drug labeling is necessary if consumers and prescribers are to have confidence that generic drugs are as safe and effective as the reference brand name product.

Finally, FDA has admitted that the proposed changes will open generic manufacturers up to greater liability under state tort lawsuits. The added costs of litigation will also cause generic prices to rise exponentially.

I thank all of our witnesses for being here today to discuss these important issues, and I look forward to your testimony.

Thank you, and I yield the remainder of my time to _____.

Mr. BURGESS. Thank you, Mr. Chairman. And again, Dr. Woodcock, thank you for joining us this afternoon.

For the past 30 years since the passage of the Hatch-Waxman amendments to the Food, Drug, and Cosmetic Act, a framework based on sameness between generic and brand name labeling has existed. Those amendments to the Food, Drug, and Cosmetic Act successfully created a safe and effective means by which safety information is relayed to the public. The Food and Drug Administration's proposed rule has the potential to upend three decades of stability, and unfortunately, upend the stability in a process that is working and working well. Allowing generic manufacturers to update safety labels unilaterally will lead to a fragmented system where confusion will abound. Multiple versions of important safety information existing for the same drug will result in confusion for patients and providers alike.

As a doctor, when I prescribe a drug, brand or generic, I want to know what the indications and risks are, I want to know that a generic is truly a generic with the same indications and the same side effects of the brand. If I am not sure, then why not just prescribe the brand drug and never mind about the cost savings?

Mr. Chairman, if patients and doctors don't have the certainty the benefits of utilizing generics, including cost savings could very well be at risk. Confusion extending to patients and pharmacists will accomplish nothing and could lead to an increase in issues with prescribing medication and the overall health of our beneficiaries. This appears to be the latest in a string of proposed rules

in which the Administration is seeking a solution for a problem that simply does not exist. Safety is paramount.

I thank the chairman for holding the hearing and I will yield back the balance of my time.

Mr. PITTS. The chair thanks the gentleman and recognizes the ranking member, Mr. Pallone, 5 minutes for an opening statement.

OPENING STATEMENT OF HON. FRANK PALLONE, JR., A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

Mr. PALLONE. Thank you, Chairman Pitts, for having this hearing.

The issue regarding generic drug labeling and its impact on patient safety is an important one and merits a thoughtful discussion. Hatch-Waxman is a true success story, one of the many that my colleague, Mr. Waxman, has been part of in his great career here. And because of this groundbreaking law passed 30 years ago, the drug market has transformed.

Today, more than 80 percent of all drugs dispensed are generic drugs. In fact, for 45 percent of generics sold, no branded product is currently on the market. So I think we all agree that this is a good thing for patients and payers.

But despite this reality, the FDA's regulation over the way in which generic drugs are labeled has remained unchanged, and I believe that in order for consumers and doctors to have confidence in the drugs that they take and prescribe, the FDA should facilitate a process which ensures that the responsibilities upon drug manufacturers reflect the current marketplace.

Last November, FDA proposed a regulation that would allow makers of generic drugs to update safety labels independently without waiting for FDA approval to reflect new information on safety issues. This is identical to the process that brand name drugs use to communicate safety issues as timely as possible. This proposal is also the result of a troubling decision by the Supreme Court in 2011 that generic drug manufacturers cannot be held liable under state tort law for an inadequate labeling, and therefore, patients who have been injured by inadequately labeled drugs have no recourse in court.

Being able to hold manufacturers accountable for maintaining adequate labeling through the court system is an important added layer of a consumer protection. And what you will hear directly from the law's author is that Congress never intended to give generic drug companies immunity from liability. In fact, prior to 2011, they did not get immunity. And so I appreciate that FDA's proposal would address this interest. I agree that something needs to be done.

Today, we will hear from critics about the consequences of the proposed regulation, in particular, that it will lead to over-warning, higher generic drug prices, and the potential for some companies to even stop making certain drug products. These are bold claims so I am interested in better understanding the basis for their views.

I believe the FDA has taken a critical step forward for patient safety but I do have questions about FDA's approach. One issue in

particular is that of sameness. Hatch-Waxman established the important principle of sameness for generic drugs relative to their branded counterparts and this principle is significant in many ways, not the least of which is to ensure consumer confidence that generic drugs are just as safe and efficacious as brand name drugs. So I am interested in learning more about FDA's consideration of the sameness principle, in particular, how such temporary differences in labeling as a result of this proposal may impinge on the benefits afforded by sameness.

And, Mr. Chairman, this is a proposed rule, like with all other regulations, FDA will and should take a serious look at the many comments that they are sure to receive. But I want to make no mistake about it; I do support their efforts. In today's marketplace, consumers must have confidence in the generic drug industry and I look forward to our witnesses' testimony and I thank them for their participation.

And I would yield back at this time.

Mr. PITTS. The chair thanks the gentleman and now recognizes the ranking member of the full committee, Mr. Waxman, for 5 minutes for an opening statement.

OPENING STATEMENT OF HON. HENRY A. WAXMAN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mr. WAXMAN. Thank you, Mr. Chairman.

Ordinarily, you would go to your side of the aisle? Oh, I see. OK.

It has been 30 years since enactment of the Hatch-Waxman generic drug law. This law has been a tremendous success if I don't say so myself. Over 80 percent of prescriptions in the United States are generic. Consumers and payers have saved over $1 trillion over the last decade alone.

Today, we are looking at one aspect of this law, and in particular, in light of the proposed rule by the Food and Drug Administration, to give generic drug manufacturers the same rights and responsibilities as brand name drug manufacturers to temporarily update safety information in their labeling without waiting for FDA approval.

The proposed rule, if finalized in its current form, would be an important step forward for patient safety. It would remove obstacles to getting new safety information about drugs to doctors and patients at the earliest possible time. It would also restore the added incentive provided by state tort liability for generic manufacturers to comply with their obligations to conduct robust post-market monitoring and to keep their drug labels accurate and up-to-date. And it would restore the ability of patients harmed by taking an inadequately labeled generic drug to pursue redress through the courts just as they were able to do before the Pliva v. Mensing Supreme Court decision in June 2011.

Now, critics of the proposed rule have argued that it will lead to over-warning. They have argued that it will result in higher generic drug prices. They have argued that it will drive generic drug companies out of business or cause them to stop making certain products. And they have argued that it conflicts with the sameness required in the Hatch-Waxman Act.

I don't believe those claims. We have heard the exact same claims about over-warning and drug company economic distress 6 years ago when the Supreme Court decided in Wyeth v. Levine cases. The Court ruled that the FDA regulation did not shield drug manufacturers from state failure-to-warn tort liability, but since then, we have not seen any of these dire predictions come to pass.

When we enacted the Hatch-Waxman bill in 1984, we did not give generic drug companies immunity from liability. In fact, the industry did not get immunity until 2011 when this Pliva case was decided. The tremendous growth of generic drugs from '84 to 2011 proved that the generic drug industry can flourish without immunity from state liability.

The one issue for which I do have some limited sympathy is that of sameness. Sameness is fundamental to Hatch-Waxman. Generic drugs are the same as their brand counterparts. They are proved based on demonstration that they are chemically the same and have the same effects in the body. And because they are the same, they are required to have the same labeling as the brand at the time of approval.

It is also important that the labels remain the same thereafter. But this does not mean that there can be no differences. There can be differences for brief periods of time when labeling updates need to be made, just as there can be because of differences in inactive ingredients or indications. In fact, the existing regulatory policy under which brands may update their safety labeling without waiting for FDA approval also results in temporary differences between the brand and generic label. These temporary differences occur during the time between when the brand makes its label change and the time when FDA approves it and then the generic manufacturer actually makes conforming changes. Few would argue that the current process violates the sameness requirements.

FDA has tried in its proposal to minimize these differences to the extent possible. Experience will tell us whether the mechanics of the process FDA has proposed will need to be improved. If refinements are needed, I hope the FDA will make them. But I applaud FDA for releasing this proposal now and urge the agency to finalize it quickly after reviewing and taking into account all the comments. I believe the rule will result in even greater consumer trust and confidence in the generic industry, trust and confidence that I am very proud to share.

I thank the chairman for holding this hearing. I look forward to the testimony of the witnesses. I yield back the time.

Mr. PITTS. The chair thanks the gentleman.

All the other members' opening statements will be made part of the record.

[The prepared statement of Mr. Upton follows:]

PREPARED STATEMENT OF HON. FRED UPTON

In a bicameral letter sent earlier this year, my colleagues and I raised important questions and concerns regarding the Food and Drug Administration's recent proposed rule on generic drug labeling, and today I hope we can learn more about the agency's rationale. There are significant concerns regarding the legal basis for the proposed rule and its consequences on patients and providers.

First, there is the question of whether FDA has the authority to even make this proposal. Since the passage of the Hatch-Waxman Act three decades ago, the agency

has adamantly asserted that a generic drug must have the same labeling as the brand-name product and that this ongoing requirement is based in statute. In 2011, the Supreme Court agreed. With this proposed rule, FDA is taking a different view of the statute. If the law does actually need to be changed for whatever reason, the authority to do so belongs to Congress.

Second, we want to find out why the FDA proposed this rule and who was involved in the decision-making process. FDA stated in the proposal that the generic market has matured and that manufacturers no longer have sufficient incentives to conduct post-market surveillance, evaluation, and reporting. They cited the need to get new safety-related information to patients faster and that allowing generic companies to change their labeling prior to FDA-approval would ensure that such companies actively participated in the process. Yet in their response to our letter from January, FDA cited no evidence that generics are not actively participating already and no evidence that there are public health concerns justifying such a fundamental shift in well-established policy. The agency made very contradictory statements in its brief to the Supreme Court just three years ago. What changed?

Finally, and most importantly, we need to understand how this proposal would impact patients and providers both in terms of confusing warnings and raising the costs of generic drugs. Generic drugmakers like Perrigo in southwest Michigan provide medicines that countless Americans depend on. In fact, more than 80 percent of prescriptions are currently filled with generic drugs. But the FDA's proposed rule could drive the costs up for the drug manufacturers, patients, and the government.

Simply, this proposed rule reverses years of successful practice and is built on questionable legal terms.

I look forward to hearing from FDA and understanding the need for and rationale behind this proposed rule. I yield the remainder of my time to _____.

Mr. PITTS. We have two panels before us today, and on our first panel we have Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

Thank you for coming today, Dr. Woodcock. Your written testimony will be made part of the record and you will have 5 minutes to summarize your testimony.

So at this time, the chair recognizes Dr. Woodcock for 5 minutes for an opening statement.

STATEMENT OF JANET WOODCOCK, M.D., DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD AND DRUG ADMINISTRATION

Dr. WOODCOCK. Thank you, Mr. Chairman, and members of the subcommittee.

I am Janet Woodcock, Director of the FDA's Center for Drug Evaluation and Research. And I appreciate the opportunity to testify.

I am happy to discuss FDA's proposed rule that would provide generic drug makers with the same opportunity as brand drug makers to update their labels when they have new safety information. They would also be able to distribute the revised label before FDA reviewed it by submitting a Changes Being Effected supplement. It is known as a CBE supplement. This would be dissemination of new drug safety information to health professionals and patients.

Now, this is a proposed rule. The comment period closed about 2 weeks ago and we are now reviewing comments. While I am free to discuss the proposal, I am not able to discuss what we may or may not do further.

FDA-approved generic drugs are copies of brand drugs. They have the same safety and effectiveness as brand drugs for their approved indications. They are held to the same quality standards as

brand drugs, and generic drug makers right now have the same obligation to monitor their drug safety as the brand drug makers do. But currently, only the brand drug makers can update their label with new safety information and distribute the revised label before FDA reviews the change. They do this by submitting a CBE supplement. Generic drug makers must wait to change their labels until the FDA approves the brand name change.

In today's world when over 80 percent of all U S. prescription drugs dispensed are generics and brand drug makers may drop out of the market after generics are approved, FDA believes it is time to provide generic drug makers with the means to promptly update their labels. In fact, for over 400 drugs, the only marketed drugs are generics and we expect that this number will increase over time.

The proposed rule, if finalized, would allow the generic drug makers to use the same process that brand drug makers use to update their safety information. It would ensure that all manufacturers marketing the drug, other generics as well as the brand, would be promptly advised of the new safety information.

And we also propose to establish a dedicated web page where FDA would post information about these proposed changes submitted in CBE supplements for all drug and biological products so that healthcare providers and patients could have access to this information while FDA is reviewing it.

FDA would make an approval decision on the proposed change for the generic drug and the corresponding brand drug at the same time so that after FDA approved a change, the brand and generic drugs would all have the same FDA-approved label. After FDA approves a label change for the brand drug, the proposed rule would set up a 30-day time frame in which the generic drug makers would submit conforming changes to their label. Right now, the situation is FDA currently advises generic drug makers to update their drug labels at the very earliest time possible after a change to the innovator, and the time in which they actually do update that varies quite a bit.

So in light of that range of time frames where generic drug makers currently submit supplements, the proposed procedures would likely minimize the current variation between brand and generic labels that is in existence right now and would cause I think less confusion because there are no time frames stipulated by FDA and there are often considerable delays before all the generic drug labels are dated. Therefore, any confusion that might be caused by different labels would be reduced by this proposal.

In conclusion, I want to emphasize that this proposed rule, if finalized, is intended to improve the communication of important drug safety information to both prescribers and patients.

Thank you and I look forward to answering questions.

[The prepared statement of Dr. Woodcock follows:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

STATEMENT

OF

JANET WOODCOCK, M.D.

DIRECTOR, CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

"EXAMINING CONCERNS REGARDING FDA'S PROPOSED CHANGES TO GENERIC DRUG LABELING"

April 1, 2014

RELEASE ONLY UPON DELIVERY

INTRODUCTION

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss FDA's proposed labeling rule which, if finalized, would speed the dissemination of new safety information about generic drugs to health professionals and patients by allowing generic drug makers to use the same process as brand drug manufacturers to update safety information in the drug product labeling. I should emphasize at the outset that this is a proposed rule and that FDA received comments on the proposal until March 13 of this year. We will consider those comments carefully, and the final rule may differ in some respects from the proposal to reflect public comments. While I am free to discuss the specifics of the proposal, I am not at liberty to discuss what we may or may not do when we issue a final rule.

FDA-approved generic drugs are copies of brand drugs and are the same as those brand-name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Generic drug manufacturing and packaging sites must pass the same quality standards as those of brand-name drugs. Generic drug manufacturers have the same requirements as brand drug manufacturers to develop written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA. More than 80 percent of all prescription drugs dispensed in the United States are for generic drug products.

Purpose of the Proposed Regulatory Action

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 301 et seq.) and the Public Health Service Act (the PHS Act) (42 U.S.C. 201 et seq.) provide FDA with authority over the labeling for drugs and biological products and authorize the Agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for those products. As you know, on November 13, 2013, FDA issued a proposed rule to amend its regulations to revise and clarify procedures for application holders to change the labeling of an approved drug or biological product to reflect certain types of newly acquired information in advance of FDA's review of the change through a "changes being effected" (CBE-0) supplement.[1] The proposed rule would create parity among application holders, with respect to these safety-related labeling changes, by permitting generic drug application holders (abbreviated new drug application (ANDA) holders) to distribute revised generic drug labeling that describes newly acquired safety-related information and, thus, may differ in certain respects, on a temporary basis, from the corresponding brand drug (the reference listed drug (RLD)) labeling at the time that the generic drug application holder submits a CBE-0 supplement to FDA. The proposed rule recognizes the obligation of all drug application holders to monitor safety information about the drugs they market and ensure that product labeling is accurate and up to date, and proposes a pathway to ensure that all drug application holders can fulfill that obligation and communicate important new safety information to prescribers and consumers. As noted, FDA sought comments from the public on the proposed rule, and the comment period closed on March 13, 2014.

[1] See "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," published in the *Federal Register* on November 13, 2013, and available online at *http://federalregister.gov/a/2013-26799*.

Summary of the Major Provisions of the Proposed Regulatory Action

The proposed rule would enable generic drug application holders to update product labeling promptly to reflect certain types of newly acquired information related to drug safety, irrespective of whether the revised labeling differs from that of the corresponding brand drug. A generic drug application holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the application holder ("new drug application (NDA)" holder) for the corresponding brand drug at the same time that the supplement to the generic drug application is submitted to FDA, unless approval of the brand drug application has been withdrawn. This proposal would ensure that the brand drug application holder for the corresponding brand drug is promptly advised of the newly acquired information that was considered to warrant the labeling change proposed for the drug in the CBE-0 supplement.

If approval of the application for the corresponding brand drug has been withdrawn (for reasons other than safety or effectiveness), FDA's evaluation of the labeling change proposed by the generic drug application holder would consider any submissions related to the proposed labeling change from any other application holder, for drug products containing the same active ingredient. The proposed rule would create that pathway for the generic drug application holder to help ensure that safety information reaches prescribers and consumers in a timely way.

When safety-related labeling updates are implemented through the CBE-0 supplement process, there may be temporary differences in drug labeling. This currently occurs when branded drug application holders update their product labelings through the CBE-0 process, and the generic

drug application holders must wait until FDA approves the change to the brand drug labeling to update generic drug labeling. Under the proposed rule, generic drug application holders would have the same ability as brand drug application holders to update product labelings with newly acquired safety-related information and FDA would reach a decision regarding the approvability of the labeling proposed by the generic and brand drug application holders regarding the safety issue at the same time.

In the current marketplace, in which approximately 80 percent of drugs dispensed are generic, and brand drug manufacturers may discontinue marketing after generic drug entry, FDA believes it is time to provide generic drug application holders with the means to update product labeling to reflect data obtained through post-marketing surveillance, even though this will result in temporary labeling differences among products. This proposed rule reflects the Agency's judgment that concerns related to temporary differences in labeling between generic drugs and their corresponding brand drugs are outweighed by the benefit to the public health, which 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.

To enhance transparency and make the safety-related changes to drug labeling described in a CBE-0 supplement readily available to prescribing health care providers and the public while FDA is reviewing the supplement, FDA proposes to establish a dedicated Web page (or, alternatively, to modify an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement.

The FDA Web page would provide information about pending CBE-0 supplements for safety-related labeling changes, including but not limited to: the active ingredient, the trade name (if any), the application holder, the date on which the supplement was submitted, a description of the proposed labeling change and source of the information supporting the proposed labeling change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study), a link to the current labeling for the drug product containing the changes being effected, and the status of the pending CBE-0 supplement (e.g., whether FDA is reviewing the proposed labeling change, has taken an action on the CBE-0 supplement, or has determined that the supplement does not meet the criteria for a CBE-0 supplement). It is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for a change to the labeling by the application holder for the corresponding brand drug, as well as other generic drug application holders. The CBE-0 supplements would remain posted on FDA's Web page until FDA has completed its review and issued an action letter. If the CBE-0 supplement is approved, the final approved labeling will be made available on the proposed FDA Web page through a link to FDA's online labeling repository at *http://labels.fda.gov*. After an adequate time period to communicate FDA's decision regarding approval of the CBE-0 labeling supplements and to facilitate submission of conforming CBE-0 supplements by other application holders, as appropriate, the original entry on FDA's Web page would be archived. Approved labeling would continue to be available at *http://labels.fda.gov*.

A supplement to an approved generic drug application for a safety-related labeling change that is submitted in a prior approval supplement or in a CBE-0 supplement would be approved upon approval of the same labeling change for the corresponding brand drug. The proposed rule

would establish a 30-day time frame in which all generic drug application holders would be required to submit a CBE-0 supplement with conforming labeling changes after FDA approval of a revision to the labeling for the corresponding brand drug. Currently, FDA advises generic drug application holders to revise product labeling to conform to the labeling of the corresponding brand drug "at the very earliest time possible."[2] In light of the range of time frames in which ANDA holders currently submit such labeling supplements, we are proposing to revise these regulations to clarify FDA's expectations regarding the time frame for submission of conforming labeling changes.

The proposed rule also would amend the regulations to allow submission of a CBE-0 labeling supplement for certain changes to the "Highlights of Prescribing Information" for drug products, with labeling in the Physician Labeling Rule (PLR) format. This is intended to remove an unnecessary impediment to prompt communication of the most important safety-related labeling changes (e.g., boxed warnings and contraindications) for drug products with labeling in the PLR format.

Finally, FDA regulations provide that FDA may take steps to withdraw approval of a generic drug application if its labeling is no longer consistent with the labeling for the corresponding brand drug, subject to certain exceptions specified in the regulations. The proposed rule would amend the regulations to add a new exception for generic drug labeling that is temporarily inconsistent with the labeling for the corresponding brand drug due to safety-related labeling changes submitted by the generic drug application holder in a CBE-0 supplement.

[2] See guidance for industry on "Revising ANDA Labeling Following Revision of the RLD Labeling" (2000).

Recent Court Decisions

In two recent cases, the United States Supreme Court considered the issue of whether Federal law preempts state law tort claims against pharmaceutical manufacturers for failing to provide adequate warnings in drug product labeling ("failure-to-warn claims") (see *Pliva, Inc.* v. *Mensing,* 131 S.Ct. 2567 (2011) and *Wyeth* v. *Levine,* 555 U.S. 555 (2009)). In *Pliva* v. *Mensing,* the Supreme Court held that the difference between brand and generic drug application holders' ability to independently change product labeling through CBE-0 supplements leads to different outcomes on whether Federal labeling requirements preempt state law failure-to-warn claims. In Wyeth v. Levine, the Supreme Court decided that Federal law does not preempt a state law failure-to-warn claim that a brand drug's labeling did not contain an adequate warning. The Supreme Court found that the drug manufacturer could have unilaterally added a stronger warning to product labeling under the CBE-0 regulation as applied to brand drug applications, and absent clear evidence that FDA would not have approved such a labeling change, it was not impossible for the manufacturer to comply with both Federal and state requirements. The Supreme Court reaffirmed that "through many amendments to the [FD&C Act] and to FDA regulations, it has remained a central premise of Federal drug regulation that the manufacturer bears responsibility for the content of its label at all times" (555 U.S. at 570-571).

Two years later, in *Pliva* v. *Mensing,* the Supreme Court decided that Federal law does preempt a state law failure-to-warn claim that a generic drug's labeling did not contain an adequate warning. The Supreme Court deferred to FDA's interpretation of its CBE-0 supplement and labeling regulations for generic drug applications and found that Federal law did not permit a generic drug manufacturer to use the CBE-0 supplement process to unilaterally strengthen

warnings in its labeling or to issue additional warnings through "Dear Health Care Professional" letters, which FDA "argues . . . qualify as 'labeling'" (131 S.Ct. at 2576). The Supreme Court found that, under the current regulatory scheme, it was impossible for a generic drug manufacturer to comply with its Federal law duty to have the same labeling as the corresponding brand drug and satisfy its state law duty to provide adequate labeling (131 S.Ct. at 2578).

As 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 a branded drug application holder, but generally not a generic drug application holder, and thus, access to the courts is dependent on whether an individual is dispensed a brand-name or generic drug. The *Mensing* decision 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.

We are proposing to change our regulations to expressly provide that generic drug application holders may distribute revised labeling that differs from the corresponding brand drug upon submission of a CBE-0 supplement to FDA. FDA's proposed revisions to its regulations would create parity between branded drug application holders and generic drug application holders with respect to submission of CBE-0 supplements for safety-related labeling changes based on newly acquired information. This proposal is also intended to ensure that generic drug companies actively participate with FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling in accordance with current regulatory requirements. If this proposed regulatory change is adopted, it may eliminate the preemption of certain failure-to-warn claims, with respect to generic drugs.

Legal Authority

The FD&C Act (21 U.S.C. 301 et seq.) and the PHS Act (42 U.S.C. 201 et seq.) provide FDA with authority over the labeling for drugs and biological products, and authorize the Agency to enact regulations to facilitate FDA's review and approval of applications regarding the labeling for those products. Section 502 of the FD&C Act (21 U.S.C. 352) provides that a drug or biological product will be considered misbranded if, among other things, the labeling for the product is false or misleading (21 U.S.C. 352(a); see also 42 U.S.C. 262(j)). Under section 502(f) of the FD&C Act, a product is misbranded unless its labeling bears adequate directions for use, including adequate warnings against, among other things, unsafe dosage, methods, duration of administration, or application. Moreover, under section 502(j) of the FD&C Act, a product is misbranded if it is dangerous to health when used in the manner prescribed, recommended, or suggested in its labeling.

In addition to the misbranding provisions, the premarket approval provisions of the FD&C Act authorize FDA to require that product labeling provide adequate information to permit safe and effective use of the product. Under section 505(c) of the FD&C Act (21 U.S.C. 355), FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Under section 505(j) of the FD&C Act, FDA will approve an ANDA only if the drug is, with limited exceptions, the same as a drug previously approved under section 505(c) of the FD&C Act, with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics, and is bioequivalent to the RLD.

Section 351 of the PHS Act (42 U.S.C. 262) provides additional legal authority for the Agency to regulate the labeling of biological products. Licenses for biological products are to be issued only upon a showing that the biological product is safe, pure, and potent (42 U.S.C. 262(a)). Section 351(b) of the PHS Act prohibits any person from falsely labeling any package or container of a biological product. FDA's regulations in 21 CFR part 201 apply to all prescription drug products, including biological products.

In addition, section 701(a) of the FD&C Act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the FD&C Act. FDA's regulations relating to CBE-0 supplements are supported by this provision. In 1965, FDA determined that, in the interest of drug safety, manufacturers should make certain safety-related changes to their product labeling at the earliest possible time.[3] Thus, for nearly 50 years, FDA, as the Agency entrusted with administration and enforcement of the FD&C Act and the protection and promotion of the public health, has required NDA holders, and subsequently biologics license application holders, to update drug product labeling with important, newly acquired safety information through submission of a CBE-0 supplement.

FDA's authority to extend the CBE-0 supplement process for safety-related labeling changes to generic drug application holders arises from the same authority under which our regulations relating to branded drug application holders and biologics license application holders were issued.

[3] See 30 FR 993, January 30, 1965.

CONCLUSION

In conclusion, I want to emphasize that this proposed rule, if finalized, *is intended to improve the communication of important drug safety information about generic drugs to both prescribers and patients.* We look forward to reviewing comments to the proposed rule. As noted previously, the comment period closed on March 13, 2014. Because there is a pending rulemaking at FDA concerning these issues, I may have to limit my response to your questions. I will try to answer any questions you may have. Thank you.

Mr. PITTS. The chair thanks the gentlelady and I will begin the questioning and recognize myself 5 minutes for that purpose.

Dr. Woodcock, in 2011 in a brief submitted to the Supreme Court in Pliva v. Mensing, FDA argued on the merits, and both the majority and dissenting opinions agreed that a generic manufacturer could not unilaterally change its labeling without violating the plain language of Hatch-Waxman. FDA has taken this position for more than 20 years over the course of various administrations.

FDA argued in the 2011 brief that generics do however have a duty to provide adequate warnings and that they discharged this duty by promptly contacting the agency about new safety information so that FDA can make an informed decision about any labeling changes the agency determines are warranted.

Without citing any evidence in the proposed rule or in the agency's response to the bicameral letter we sent in January, FDA now speculates that generic companies will stop meeting their post-market requirements under the law. Despite all their previous assertions to the contrary and despite the fact that they took the exact opposite position in 2011, FDA is now claiming that the Hatch-Waxman Act does not in fact preclude a generic company from unilaterally changing their labeling to strengthen warnings, that they should now be able to do so because the market has matured.

Dr. Woodcock, the market has not matured all that much since 2011. What really prompted the FDA's decision to fundamentally change its position on these matters and what role did plaintiffs' lawyers play in the process?

Dr. WOODCOCK. What prompted FDA to look into this rule was partly by the court ruling that pointed out a disparity in the obligations between the generics and the innovator drugs. And in today's world, a world where the generics are more than 80 percent of all prescriptions dispensed to patients in this country, we feel the standards should be the same, the standards for manufacturing, the standards for safety and efficacy, the standards for overseeing safety, and the standards for reporting to FDA. So we wanted to have a level playing field, have the same standards, and correct this inconsistency.

Mr. PITTS. Now, in February of 2013 while FDA was drafting this proposed rule, agency officials met with several plaintiffs' lawyers, including at least one representative from the American Association for Justice, also known as the Association of Trial Lawyers of America. In fact, according to FDA's public calendar, one of the agency participants in this meeting was Daniel Siegelman from the office of the Commissioner, who is himself a former prominent member of trial bar. Would you please provide the Committee with the minutes from this February 2013 meeting?

Dr. WOODCOCK. We will get back to you with what we have.

Mr. PITTS. Would you commit to working with the Committee to provide any other communications between agency officials, including Mr. Siegelman and representatives of the American Association for Justice relating to the proposed rule or other approaches that were considered?

Dr. WOODCOCK. Certainly.

Mr. PITTS. Now, I am going to read a statement from a separate brief submitted to the Supreme Court by Ranking Member Wax-

man and ask you to comment. "It is clear that a generic and a brand name label must be the same and that a generic firm cannot unilaterally change its label. To permit individual generic drug labels to differ significantly from their brand name counterparts, particularly with respect to safety information, would thwart the sameness goal reflected in the Hatch-Waxman amendments." Dr. Woodcock, did the agency agree with this statement in 2011 and does the agency agree with this statement today?

Dr. WOODCOCK. All right. Certainly with all due respect to Mr. Waxman, who has obviously authored the legislation, I would like to dispel the notion that the labels are the same now with respect to safety information.

We have looked at this and it is not just the CBE–0, but when we, say, do a class labeling, say, for the NSAIDs, we put a box warning in, some major safety change is put into drug labels, there is a time frame that can be considerable under which the generics submit conforming labeling. And during that time frame, those labels are different.

And in fact, I would submit to you from a practical point of view as I administer the program, these drug labels are dynamic and may change up to maybe 10 years, 15 years. I think our latest is 38 years after a drug has been on the market, we are still discovering safety information. That needs to get onto the label as quickly as possible. The generic copies may take quite a long time, months, perhaps a year or so before they make conforming changes to their label. And then of course that takes much longer to get out there in circulation because the print nature of the package insert.

So, while in principle they are the same, because of the dynamic nature, they are not literally and exactly the same right now. And the proposed rule, if it were enacted, would actually narrow down that time, that disparity, that temporary difference. And after FDA would approve, maybe we would not put the safety label in or maybe we would decide that the safety update goes on a drug label, then all the manufacturers of that drug would have to change and the generics would have 30 days in which to do that.

Mr. PITTS. The chair thanks the gentlelady and now recognizes the ranking member, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

Dr. Woodcock, Mr. Neas, who is here today representing the generic drug makers, argues that FDA should focus on assuring patient safety and not on preemption of state tort law. I agree with the FDA that state tort law complements FDA oversight and enhances patient safety. My reading of the FDA proposed rule is that its primary purpose is to realign FDA post-market safety monitoring and labeling requirements with the realities of the current marketplace and increase the speed at which new drug safety information gets to doctors and patients.

So I just wanted to ask you initially is that a fair reading of the purpose of the proposed rule and if you wanted to comment on that?

Dr. WOODCOCK. That is correct. With over 80 percent, as we have all said, of drugs taken by Americans today being generic drugs and many of the generic drugs not having an innovator copy on the market, the goal is to make sure that the whole system is search-

ing for safety problems and promptly updating labels when they are found.

Mr. PALLONE. So another criticism made by Mr. Neas is that requiring generic manufacturers to make unilateral labeling changes will lead to a flood of unnecessary and different labeling changes and confuse doctors and patients. And he also claims that companies will exaggerate the risks of their drugs leaving patients to avoid taking needed medications.

I know that in the lead up to the Wyeth vs. Levine case, brand drug companies made similar predictions of over-warning if the Supreme Court were to rule again preemption, as it did.

So I guess, couple things. First, has FDA found that drug companies commonly over-warn?

Dr. WOODCOCK. Well, we have existing precautions against that. Our regulations that we passed a few years ago called the physician labeling rule, which modernized the drug package insert, has specific caveats about doing such things and requires certain levels of evidence before you just put warnings in the label. Many of you may not have looked at a drug label, but long ago, they were what we called the laundry list. There were just long lists of things that might happen to you. And the modern drug label has eliminated much of that because it is not informative.

Mr. PALLONE. Did the FDA see a worrisome increase in over-warning after Wyeth v. Levine?

Dr. WOODCOCK. Not to my knowledge.

Mr. PALLONE. And the FDA believes that this concern about the over-warning, do you think that is warranted?

Dr. WOODCOCK. I think it is important to stress that these warnings are temporary. They are put up there because something has been discovered and the company feels there is a reasonable link to the drug. Then after that occurs, right now with the innovator, we take a look at that and we gather up whatever evidence there might be and we may have studies or other things that are brought to bear. And then FDA makes a decision about whether that is actually going to be approved FDA labeling or not. And the same would be true here with this proposal.

Mr. PALLONE. All right. Let me ask you about the Mensing decision. Were generic drug companies subject to failure-to-warn liability before Mensing?

Dr. WOODCOCK. Well, first of all, may I remind everyone I am not a lawyer; I am a physician. But I understand that for many years prior to the Mensing decision, the generic drug manufacturers were generally considered to be potentially liable for failing to warn of important drug safety information. And during that time, they grew to about 75 percent of the U.S. retail prescription market. In other words, the industry thrived during that time.

Mr. PALLONE. So is it fair to assume that finalizing the FDA rule essentially will bring the generic industry's liability situation back to something similar to what they faced before the Mensing decision in 2011?

Dr. WOODCOCK. I think that is a reasonable assumption that I would again argue that I am not very qualified to opine on that.

Mr. PALLONE. I mean because we have all heard that—well, I guess the GPhA commissioned a study looking into the economic

impact of the FDA rule, and it concluded that finalizing the FDA rule will lead to new liability protection costs for the generic drug industry of about $4 billion a year, and yet the cost attributable to the FDA rule sound like they may be, you know, really not different from the liability cost the industry faced prior to Mensing. So, I don't. I am questioning the value of the study. You don't have any comment?

Dr. WOODCOCK. It requires a lot of assumptions to make those conclusions.

Mr. PALLONE. All right. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Thank you, Mr. Chairman. Thank you, Dr. Woodcock. I appreciate it very much. Thanks for your testimony.

First question, depending on the drug, there could be a dozen generic products for the same brand drug. From a public health stand point, don't you believe that the multiple different versions of labeling will lead to confusion among doctors?

Dr. WOODCOCK. Well, in fact, the state is now when FDA makes a label change to the innovator, there will be multiple different versions because the generic drugs will be changing. We have seen the drug makers will change their label over a period of time. Some would change their label to conform very rapidly; others may take a year or so. So that is the current situation.

Mr. BILIRAKIS. OK. Next question: the FDA frequently issues guidance documents better informing industry of FDA's expectations. How many guidance documents has FDA issued related to updating of generic drug labeling in the past decade? Can you give me that information?

Dr. WOODCOCK. I can't but I could get back to you on it.

Mr. BILIRAKIS. Please do.

Isn't it true that the FDA currently has the regulatory authority to set specific time frames within which a generic company must update their labeling to conform to the brand name equivalent, and doesn't FDA have the authority to take regulatory action against any company that doesn't comply with the agency's requirements?

Dr. WOODCOCK. For the second part of your question, do we have the ability to take action? Yes, I believe we do. And for the first part of your question, that is part of this rule. The proposed rule stipulates a time frame in which the generics would have to conform. So we do have that ability. We show that by proposing this rule.

Mr. BILIRAKIS. OK. If FDA feels as though it is not getting adequate post-market safety information from companies——

Dr. WOODCOCK. Yes.

Mr. BILIRAKIS [continuing]. As required under the law, isn't it the agency's responsibility to better enforce these requirements to ensure that it does?

Dr. WOODCOCK. Well, I think that is a more complicated question. It is a very complicated question. This proposed rule is about giving companies the ability to rapidly change their label and communicate information that they have found, all right. Generic drug companies do not frequently submit new safety information to the FDA.

What we usually audit companies for is their required apparatus that they have to monitor for safety and to report to us to make sure that they operate those functions. For example, for a generic drug where there was no innovator on the market anymore, we would really like to know that the generic drug companies were out there watching and seeing what is happening with their drug and telling us if they come across any new safety problems.

Mr. BILIRAKIS. OK. Thank you.

I yield back, Mr. Chairman. Thank you.

Mr. PITTS. The chair thanks the gentleman and now yields to the ranking member of the full committee, Mr. Waxman, 5 minutes for questions.

Mr. WAXMAN. Thank you, Mr. Chairman.

I feel like I am in a Woody Allen movie when they asked about Marshall McLuhan and the man in the back of the line said I am Marshall McLuhan and everything you said is absolutely wrong. Well, I am Henry Waxman from the Hatch-Waxman and I am here to set the record straight.

I submitted a brief to the Supreme Court and I stated generic and brand name labels must be the same because, after all, the generic drug has to be the same as the brand name drug so the warning labels have to be the same. But that was in the context of the existing FDA regulation that said the brand name companies could change their label if they know something more that they ought to tell the consumer, but the generic companies could not change their label and they couldn't act unilaterally.

So I was making the point that even within that context, generic manufacturers should be subject to the state failure-to-warn tort liability. That was my argument. The Court didn't accept it. The Court said you have FDA regulations and what we were arguing was not consistent with them. Now you are proposing a new regulation.

My amicus also contained the statement that to permit generic labels to differ significantly from their brand counterparts, particularly with respect to safety information, would thwart the sameness goal reflected by the Hatch-Waxman Act. So I still believe that to be true. However, I don't think allowing a temporary period of time in which the labels may be different thwarts the sameness goals.

For example, you have existing regulations called CBE–0, and that allows the brand name company, when they learn some problem, to change their label even if FDA doesn't approve it. FDA may later approve it. They have to send it to FDA, but they can act on their own unilaterally. That would mean the warning label would be different than on the generic drug, isn't that right, Dr. Woodcock?

Dr. WOODCOCK. That is correct. And also the generics may take various amounts of time even when FDA has approved a label change to conform their own label.

Mr. WAXMAN. So we have a period in time I would like to be kept at a minimum before the labels are the same but there is a difference in time, and no one would argue that that violates the Hatch-Waxman Act.

Dr. WOODCOCK. Yes.

Mr. WAXMAN. Sameness in labeling is important but also finding out about new problems is important. You mentioned an example to Mr. Bilirakis. What if the generic was based on a brand that is no longer on the market?

Dr. WOODCOCK. Yes.

Mr. WAXMAN. Would we prohibit a generic that learns about problems from doing anything to warn the public about these problems? I think that was one of the issues that you had in mind in proposing this new regulation, isn't that right?

Dr. WOODCOCK. That is correct. And increasingly, the innovator companies are concentrating on innovation——

Mr. WAXMAN. Yes.

Dr. WOODCOCK [continuing]. And dropping their drug or withdrawing it from the market or even withdrawing their application after the drug goes generic because they can't compete or they don't want to compete in that space.

Mr. WAXMAN. Yes.

Dr. WOODCOCK. And so there the generics are responsible. They must stand behind that drug because there is no one else watching the safety of that medication other than, of course, the FDA.

Mr. WAXMAN. The FDA but the generic manufacturers which may be the only manufacturers of the drug are more likely to hear about the problems for which they need to warn the public and hopefully they will give that to FDA. But they are the ones that are making the drug that could be harmful unless people understand the warnings that should go with it, isn't that right?

Dr. WOODCOCK. That is correct. And most of the reports we get—we get about 1 million reports a year about drug safety problems and about 80 percent of those are from the manufacturers.

Mr. WAXMAN. Yes. OK.

So I think there needs to be sameness in labeling. I think that is critical, but equally important is ensuring the patients know they will have the same right to access courts whether they are injured by taking a generic drug as they would if they took a brand drug. We don't want to scare consumers to think, oh, if I take a generic, I may be taking something that is not as safe. That has always been the brand name industry's claim, that it is not the same; it is not as safe. But of course if they are the same and the warnings are the same, then the consumers should relax. And we want to get to that same labeling.

Mr. Neas and Mr. Shumsky claimed that the proposed rule fundamentally violates the sameness principle and that it undermines the statutory and regulatory framework for approving and overseeing generic drugs. How do you respond to that, Dr. Woodcock? There are differences that occur now between brand and generics. When brands use their existing CBE–0 process to update their safety labeling, what you would be doing is giving the generic that same opportunity. Do you think that this is going to mean that we are going to have less sameness in drug labeling?

Dr. WOODCOCK. I believe the portions of the rule that call for the webpage and then call for all the labels to be conformed within 30 days will result in less differences among brand and generic labels in the future if this rule were to be made final.

Mr. WAXMAN. That is a good objective.

Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman. And good afternoon, Dr. Woodcock.

This is a very complicated topic. As I understand the recent Supreme Court decisions, there is a question legally as to whether the proposed rule complies with those decisions. I certainly want the public to be as safe as possible, and at the same time, I don't want the public to be confused. Do you see any potential of a conflict between safety, which we all desire, and confusion among the public on this issue?

Dr. WOODCOCK. Well, as we have been talking about a little bit, I believe if the proposed rule were implemented, it would reduce confusion caused by differing labels because there would be more conformity of labels.

Mr. LANCE. As I read the underlying statute, it appears to me to be clear and it is my own opinion that what is proposed may go beyond what is currently in the underlying statute. And obviously, agencies try to administer underlying statutory law to the best of your ability given your responsibilities in the executive branch. Would it have been better for the agency to come to us here to Congress to ask for an amendment if you thought that you needed to move forward in the way you are apparently moving forward?

Dr. WOODCOCK. It is hard for me to speculate on that. I am not a lawyer. I would say that——

Mr. LANCE. That speaks well of you. Some of us are lawyers.

Dr. WOODCOCK. Well, I don't, opine as a lawyer. I am not one. However, I will say that we have been administering this program a long time. The generic drug labels are actually different in many areas, some of which have been stipulated by Congress. For example, pediatric——

Mr. LANCE. Yes.

Dr. WOODCOCK [continuing]. Exclusivity and et cetera, et cetera. And they are different in their safety information due to the time frame often it takes and due to the fact that the generic industry does not often update their label in a timely manner.

Mr. LANCE. Thank you. I would hope that on issues like this the executive branch and the legislative branch could work together and often where you stand on an important issue of public policy is based upon where you sit and sitting in the legislative branch of government and having reviewed the underlying statute and certainly having a great respect for those who wrote the statute, including Mr. Waxman, I tend to view the opinion of Mr. Shumsky and others as how I would read the underlying statute. I realize it is extremely complicated. But I would prefer if the executive branch and the various agencies might come to us if an amendment would clarify the situation and certainly statutory law from my perspective serving in the Congress is the bedrock by which agencies proceed, recognizing as I do that the safety and health of the American people is preeminent.

Thank you, Mr. Chairman, and I yield back the balance of my time.

Mr. PITTS. The chair thanks the gentleman and at this time recognizes the gentlelady from Virgin Islands, Dr. Christensen, for 5 minutes for questions.

Mrs. CHRISTENSEN. Thank you, Mr. Chairman. Welcome back, Dr. Woodcock.

Dr. Woodcock, FDA describes both the existing and the proposed CBE–0 processes as an exercise of enforcement discretion, and that sounds like either the agency is deliberately flouting the will of Congress or the law is so badly written that FDA can only make it work by ignoring parts of it. Yet I know that FDA uses enforcement discretion in many areas of regulation with good effect.

Could you put your use of enforcement discretion in the CBE regulations into context? Could you explain how the agency uses it elsewhere and its oversight of drugs or other FDA-related products and why you have chosen to use it in this instance to allow drug manufacturers to rapidly update their safety information?

Dr. WOODCOCK. Well, first of all, I understand that originally when the CBE–0 regs were written, that was how it was described a long time ago. Maybe I was in high school. But I think that what I understand from our lawyers now is that we regard this as—the statute of course sets the framework, as has just been pointed out, that regulations are implementing of that framework. We regard this as implementing, interpreting part of the statute. So I am not sure we regard this in today's legal world as enforcement discretion.

But we do use enforcement discretion in many areas. For example, one of the most poignant is probably our dealing with the shortage issues where we are getting products from around the world for critical medical needs that are being not met for our population. After we verify that they are correctly manufactured and of high quality, we will have them imported into the United States.

Mrs. CHRISTENSEN. Thank you. Well, whether it is enforcement or not, I think the whole process seems consistent with one of the overriding purposes of the food and drug law, to protect patient safety.

Also in his testimony, Mr. Neas notes that generic manufacturers only have access to information about their individual products saying that FDA is the only entity with access to all safety information and is the only body in a position to decide whether a labeling change is warranted. How do you respond to those points?

Dr. WOODCOCK. Well, what we are talking about here is sort of early notification. That can be done now by the innovator to change their label in advance of an FDA decision. And what we are proposing is that the generic industry should be able to change their label in advance of an FDA decision. After we get a safety signal and, we may evaluate it through our Sentinel system, we may do a literature search, seek data from other sources, and generally deliberate and finally make a final decision. You know, should this be a box warning? Should it be a precaution? Is it a contraindication or is it just another warning? Or maybe, as was raised earlier, it isn't adequately linked and should not be on the label.

Mrs. CHRISTENSEN. Yes.

Dr. WOODCOCK. Once we make that decision, we then are proposing here that we tell everyone all at once you should change your label to conform to the FDA decision.

So, yes, FDA would weigh in at the end of the day on this but what we will do now, and as a clinician you are aware of this, and it is frustrating somewhat but FDA will put out safety information that says we are looking at this.

Mrs. CHRISTENSEN. Yes.

Dr. WOODCOCK. We just don't know what it means yet. But people became very unhappy that we weren't notifying them that we were evaluating this issue, so if it is an important safety issue, we actually put out a drug safety alert and say we are evaluating this. We don't know what the truth is yet, but we will keep you informed and let you know when we have made a decision.

Mrs. CHRISTENSEN. Thank you. And I agree basically. And as the proposal notes, not only do generic drugs now comprise over 80 percent of drugs sold but they constitute 94 percent of the market for those drugs for which generics are available. So many of them may not have a preponderance on the market. Some are likely to have much more than the brand. And as the rule makes clear, FDA continues to reserve for itself the final decision regarding proper labeling.

Thank you, Dr. Woodcock.

Dr. WOODCOCK. Thank you.

Mr. PITTS. The gentlelady yields back.

The chair recognizes the gentleman from Illinois, Mr. Shimkus, for 5 minutes for questions.

Mr. SHIMKUS. Thank you, Mr. Chairman. Welcome, Dr. Woodcock. Good to see you again.

In proposing significant changes to prescription drug labeling requirements in December 2000, FDA, under the Clinton Administration, found "the use of labeling and product liability and medical malpractice lawsuits, together with increasing litigation cost has caused manufacturers to become more cautious and include virtually all known adverse event information regardless of its importance or plausibility relationship to the drug." Do you agree with this statement or is this no longer a concern of the agency?

Dr. WOODCOCK. That was the practitioners' labeling rule, the label modernization that you are talking about. And in there we put in some standards that prevent putting in the label events that are not really causally linked where we don't see a causal association. So we were basically putting people on notice that we did not think that those types of events, that laundry list, should get into a drug label. And the modernized drug labels do not have that feature.

Mr. SHIMKUS. So it is no longer a concern of the agency?

Dr. WOODCOCK. It is always a concern but we have put in safeguards to make sure the modernized labels——

Mr. SHIMKUS. OK.

Dr. WOODCOCK [continuing]. Don't contain that.

Mr. SHIMKUS. All right. Before proposing the 2000 rule, the FDA held multiple focus groups and conducted a national survey of healthcare providers. Prior to issuing the proposed rule in November of 2013, did the FDA discuss these changes with physicians?

Dr. WOODCOCK. Yes. Well, the physicians were part of the focus groups. We had a public——

Mr. SHIMKUS. No, I am talking about this current rule that you are proposing.

Dr. WOODCOCK. Oh, this one. Oh, I am sorry. No.

Mr. SHIMKUS. Did the FDA meet with any pharmacists to hear their thoughts?

Dr. WOODCOCK. No, not to my knowledge.

Mr. SHIMKUS. Did you meet with any of the branded drug companies?

Dr. WOODCOCK. Not to my knowledge.

Mr. SHIMKUS. What about the generic drug companies?

Dr. WOODCOCK. Not to my knowledge. I did not.

Mr. SHIMKUS. Did the FDA meet with the trial lawyers?

Dr. WOODCOCK. My understanding is that this is the case. However——

Mr. SHIMKUS. So in 2000 you met with all these groups?

Dr. WOODCOCK. That is correct.

Mr. SHIMKUS. So you didn't meet with physicians, you didn't meet with pharmacists, you didn't meet with branded drug companies, you did not meet with generic drug companies, but you met with the trial lawyers?

Dr. WOODCOCK. Well, after the——

Mr. SHIMKUS. I think you have already testified it is yes.

Dr. WOODCOCK. After the court decision I sat down with the staff at the Center for Drug Evaluation and Research and we went over options for dealing with this disparity in the treatment of the two groups. And we went ahead and drafted this rule. I was not aware——

Mr. SHIMKUS. So let me get back. So the answer is yes?

Dr. WOODCOCK. My understanding is——

Mr. SHIMKUS. You can just say it. Come on. Get it out.

Dr. WOODCOCK. Part of the agency did meet with the trial lawyers, yes.

Mr. SHIMKUS. Thank you. Because in your responses earlier, you talked about how innovator drugs, right——

Dr. WOODCOCK. Yes.

Mr. SHIMKUS [continuing]. Who may not be in the market anymore and you have the generic drug——

Dr. WOODCOCK. Yes.

Mr. SHIMKUS [continuing]. But it is funny you are using that as an explanation but you didn't discuss this with innovator drugs and you didn't discuss this change with the generics. So even in your answers to our questions today, you are using what you would think would be support from and inclusive process of an evaluation of a new rule without talking to these two groups.

So let me ask you this question. What role did the trial lawyers play in complying in the development of this new rule?

Dr. WOODCOCK. To my knowledge, none, because, as I said——

Mr. SHIMKUS. Wait, wait. You met with them, you changed the rule, and you are saying they had no role in developing this new rule?

Dr. WOODCOCK. Right. I was trying to explain that.

Mr. SHIMKUS. I know. I am trying to believe it.

Dr. WOODCOCK. Well, I am explaining factually what happened, all right. The Center for Drugs, I asked our staff here at the Center for Drugs to look at this finding which pointed out we did not have a level playing field of sameness between the innovators and the generic drug firms. They developed a list of options. We picked the option we wanted to pursue and it was really a matter of feasibility and execution and we developed that rule. The personnel in the Center for Drugs did not meet with the trial lawyers——

Mr. SHIMKUS. And you understand why we have questions about this rule if you met with just the trial lawyers and you didn't meet with any of the folks that are involved in this sector?

Dr. WOODCOCK. Certainly.

Mr. SHIMKUS. All right. Thank you. I yield back my time.

Mr. PITTS. The chair thanks——

Mr. WAXMAN. Mr. Chairman, I ask unanimous consent that the gentleman be given an additional minute so I can ask him to yield to me.

Mr. PITTS. Do you want to have me recognize Mr. Sarbanes?

Mr. SHIMKUS. No, the ranking member is asking for unanimous consent for me to be given another additional minute so I can then yield to the ranking member.

Mr. PITTS. All right. The chair recognizes the gentleman for one minute.

Mr. SHIMKUS. I would be happy to. And I would then yield to Mr. Waxman.

Mr. WAXMAN. Whoever you met with before is interesting but don't you now have to have comments from everybody with a proposed rule and take those comments into consideration?

Dr. WOODCOCK. Certainly. The folks we met with before were about parts of the label that would really impact them and this is more of a procedural issue. But we put together a procedure. We instantiated it in this proposed rule and we have received over 100 comments from a wide range of groups and we will be evaluating those comments.

Mr. WAXMAN. Thank you.

Mr. SHIMKUS. And reclaiming the rest of the minute, I understand that now you are going to receive comments. However, historically, you met with everyone involved in this sector. You now issue a new proposed rule with only meeting with the trial lawyers. I think that raises cause of concern and the reason why many of these questions are going to for what purpose and there is a question on intent.

And I yield back my time.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Maryland, Mr. Sarbanes, for 5 minutes for questions.

Mr. SARBANES. Thank you, Mr. Chairman. Thank you, Dr. Woodcock. You are one of the best witnesses we get up here and I appreciate your testimony.

I am sort of baffled at what the objection could be to the proposed rule and looking forward to the second panel to elucidate that for me. It seems eminently reasonable what you are trying to do. I think that it strikes exactly the right balance that we would want to see between the objectives, aspirations, and the success of

the Hatch-Waxman Act and then having to deal with practical obstacles that that framework encounters over time. So it makes a lot of sense what is being proposed.

And Congressman Waxman got right to the point I was going to make which is I gather now that comments have been in as of 2 weeks ago, right?

Dr. WOODCOCK. Yes.

Mr. SARBANES. And those include a lot of perspective from consumer groups out there, people that are concerned about safety issues, presumably, isn't that the case?

Dr. WOODCOCK. Yes, there are comments from consumers, consumer groups.

Mr. SARBANES. It seems to me this notion that if a trial lawyer has a positive opinion of the proposal, that somehow that should taint, undermine, or eliminate the concerns that the broad public has about seeing this kind of proposal. In fact, my view would be that they are largely reflecting the opinions and perspective of the broad public and those people who could be potentially damaged if you don't have a proper framework in place. So it is good to hear that those comments include organizations that would represent that kind of perspective on safety. And we look forward to seeing how the rule will roll out from here.

I was curious before the Mensing case, before this decision that appeared to protect or did protect the generic manufacturers from failure-to-warn cases at the state level, which was only a couple of years ago. Before that, as industry was developing, presumably they were getting more engaged in monitoring based on the exposure and liability that they properly had vis-a-vis the public and consumers. Would that be accurate to say?

Dr. WOODCOCK. Yes. And as far as sameness, they have the same requirements for monitoring the recipients of their drug or any reports that they get of problems with their drug and reporting those to the FDA so that is the same as for the innovator industry.

Mr. SARBANES. You mentioned that you think probably there are some assumptions and the projection that this will result in a $4 billion hit to the generic drug industry as a result of having this liability there. I will be interested to hear testimony that backs those kinds of assumptions up because I am skeptical of them, as I think you are, and certainly Congressman Waxman has indicated his skepticism about that.

I am a very intrigued by your testimony that not only does the proposed rule not add to the sameness problem——

Dr. WOODCOCK. Yes.

Mr. SARBANES [continuing]. That has been discussed but in fact it would help to remedy——

Dr. WOODCOCK. Yes.

Mr. SARBANES [continuing]. Some of the problems that there has been with sameness because there hasn't been in place the kind of timelines that would push the generic manufacturers to come in to conformity on a more expedited basis.

Dr. WOODCOCK. That is correct.

Mr. SARBANES. So you have sameness issues now that are kind of initiated from the innovator brand side of the equation. You may now get situations where the sameness, you know, that sort of

glitch gets initiated from the generic side. But all told, what you are proposing, as I understand it, is a structure that will lead to more sameness, to use that sort of odd phrase, than less. And so that will be actually an improvement over the current situation, is that correct?

Dr. WOODCOCK. That is correct. We would anticipate that the amount of disparities between the generic label and innovator label will decrease with this proposal because it will put in a 30-day clock for conformance to the labels.

Mr. SARBANES. Terrific. Thank you very much, and I yield back.

Mr. PITTS. The chair thanks the gentleman. Because we have a just heard there may be some confusion over various views on this proposed rule, let me take this time to request unanimous consent to insert the following documents into the record: AARP letter to Commissioner Hamburg dated March 13, 2014; "The FDA's Proposed Generic Drug Labeling Rule: An Economic Assessment" by Alex Brill, February 5, 2014; a letter from FDA to Congressman Kevin Yoder, January 29, 2014; March 6, 2014, letter from 24 members of the Pharmaceutical Supply Chain to Commissioner Hamburg; of the labels on generics drugs, "The FDA Should Take the Lead on Making Drug Warning Labels Consistent," LA Times, article, March 12, 2014; committee letter to Commissioner Hamburg regarding the proposed change to generic drug labeling policy dated January 22, 2014; and the FDA's response dated February 26, 2014; a letter dated March 14, 2014, to Commissioner Hamburg from Minority Health Groups; and finally, a letter dated March 13, 2014, to Commissioner Hamburg from Patient Advocates.

Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. The chair now recognizes the gentleman from Kentucky, Mr. Guthrie, 5 minutes for questions.

Mr. GUTHRIE. Thank you, Mr. Chairman.

Thank you for coming, Dr. Woodcock.

A lot of discussion on the topic of changes being effected involves generic drugs. It occurs to me that CBE is also an important policy issue in the context of biosimilars. What is the current legal status of CBE with respect to biosimilars and would the proposed rule change the current legal status of CBE with respect to biosimilars? And I know that biosimilars, though none have been approved by the FDA yet, but when they are, will they have CBE or not?

Dr. WOODCOCK. This rule does not pertain to that because those would be under the Public Health Service Act and they are not considered generics like the generics are. So that is a separate issue.

Mr. GUTHRIE. Completely separate, thank you.

In your testimony throughout the day, you stated four or five times that this rule would address the need for outdated generic labels to be updated. While that may be so, that was not the basis for why the FDA issued the proposal. In fact, I have been told that the goal was not even addressed in the proposed rule. What is the agency's stated rationale for proposing this rule change and if updating outdated generic labels is really the goal, can't you address those administratively or with better enforcement?

Dr. WOODCOCK. Well, the goal of this, at least my goal and the Center for Drugs' goal was to update what we felt was a disparate

playing field for the brand industry and the generic industry where the generic industry has really grown up to be taking care of much of the healthcare of your constituents in this country. The drugs they get at their pharmacy are generic drugs. And so that was the goal from my point of view.

We are looking at updating old labels and this isn't just a fault of the generic industry; it is a fault of the innovator industry, too. Drug labels need to be modernized and the modernization effort that was talked about earlier only went back to, I think, 2003.

Mr. GUTHRIE. Yes.

Dr. WOODCOCK. And so we are looking at updating globally the drug labels in general.

Mr. GUTHRIE. Is your FDA pilot project Sentinel, is that focused on that? Is that what that is, the Sentinel system?

Dr. WOODCOCK. Sentinel system is using electronic health records to learn and look at safety signals that we get. So that is what Sentinel is about. We have electronic health records of 150 million people and we can look in there and find out what happens when they took a drug and find out whether a side effect is real. We are doing a different pilot on modernizing drug labels that have become out-of-date.

Mr. GUTHRIE. OK. And I have one last question. Ranking Member Waxman discussed the brief he filed with the Supreme Court in 2011. My understanding of that brief a different approach than the one ultimately included in FDA's rule proposed was raised. I believe the brief suggests that FDA should formalize the process by which a generic manufacturer could provide the FDA with any new information they obtained regarding safety hazards associated with their products and that they could be held liable if they failed to do so. Why does the FDA feel that that was an inadequate approach and why you have to go this direction?

Dr. WOODCOCK. I am sorry but I am unfamiliar with what mechanism that they were supposed to update their labels.

Mr. GUTHRIE. Yes. I have a quote from the brief. "Provide the FDA with any new information they obtain regarding safety hazards associated with their products."

Dr. WOODCOCK. Yes, well, generics have always supposed to have been able to do that. So this is simply a mechanism. This is really a procedural rule that allows a procedure that was always available to innovator to be made allowed to be available to generics as well.

Mr. GUTHRIE. OK. Thank you. I yield back.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Texas, Mr. Green, for 5 minutes for questions.

Mr. GREEN. Thank you, Mr. Chairman. And I am glad you are here, Dr. Woodcock.

I think the three main criticisms of the proposed rule is that it would restore tort liability to generic manufacturers, which I don't know if that was the intent but one criticism if the proposed rule restores the tort liability, which critics argue would lead to warning and significant higher generic drug rates.

Two, the rule undermines the sameness principle that generic and brand name drugs have to be the same, including their label-

ing and therefore undermines the entire Hatch-Waxman justification.

And three, the rule would lead to a multitude of different labels confusing doctors and patients and undermining confidence in generic drugs.

Frankly, I don't mind if somebody is producing a drug, they ought to have some responsibility for it so I don't have that big a concern about the tort liability. But the other two I do have some concern about. It undermines the sameness principle that Hatch-Waxman did and also the multitude of labeling.

Dr. WOODCOCK. Well, as I explained earlier, right now, there are different versions of the label because the innovator will change their label. Even after FDA approves that label, it takes some time, for some cases a year, maybe 2 years for some of the generics, not all of them, to change their label. So there are differences out there between the innovator and generic labels that are disparities now. And this proposal that we have would reduce the time of confusion if you want to call it confusion.

Mr. GREEN. OK. But then the sameness principle issue that was brought up?

Dr. WOODCOCK. I feel that the sameness applies and if you are a consumer or patient I think that you would want to know that the drug is the same as far as its chemical composition, as far as its pharmacology, and as far as the manufacturers standing behind that drug, all right, and doing the safety surveillance and the monitoring and keeping their label up-to-date no matter whether they are innovator or a generic manufacturer.

The sameness as a literal point of view that labels need to be exactly the same, they are not exactly the same and there are a number of reasons, for example, the pediatric exclusivity, there may be certain constituents that are slightly different that is allowed. There may be other carveouts to the label due to new indications that the innovator has that the generic doesn't have. And there are these differences due to the safety changes in other label updates that actually the generics don't necessarily update in a timely manner.

Mr. GREEN. Well, Mr. Chairman, I think consumers actually do look at labeling, too, not just physicians obviously, for the prescription.

Dr. WOODCOCK. Yes.

Mr. GREEN. And I will give you an example. Zyrtec is something that has been successful but now it has lost its exclusivity and there is a generic available for it that I noticed still has the same compounds as Zyrtec. So consumers also look at it other than physicians.

And I yield back my time.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Georgia, Dr. Gingrey, 5 minutes for questions.

Mr. GINGREY. Mr. Chairman, thank you. And, Dr. Woodcock, good to see you.

What is wrong with the current process that the FDA has defended as being necessary to bring orderly change to the labeling when it is warranted? What is wrong with the current——

Dr. WOODCOCK. As the universe has changed and time has changed, the generic industry is now in charge of much of the healthcare. It delivers most of the dispensed prescriptions in the United States.

Mr. GINGREY. Well, I know the doctor from the Virgin Islands mentioned that a little earlier, that maybe 85 percent of the drugs that are dispensed today are generic. Is that what you are getting at?

Dr. WOODCOCK. Yes. And, in fact, in that situation those manufacturers who are marketing those drugs, they need to be monitoring those drugs for safety. The people who market the drugs will get the reports, all right?

Mr. GINGREY. Let me ask you this just a yes-or-no answer. The approach the FDA now proposes will result in an orderly process that gets evidence-based appropriately tailored labeling changes to prescribers in the best possible manner.

Dr. WOODCOCK. Yes.

Mr. GINGREY. It does, right? In this proposed rule—and, listen, I just came from another committee hearing where I was praising the trial attorneys, but this proposed rule sure seems to me to be led by the trial attorneys. I am following up on what the gentleman from Illinois, Mr. Shimkus, said. And as a physician like me, I hope that you would disagree with this implication that the FDA trusts the trial bar to be the chief stewards of public health policy.

Dr. WOODCOCK. The impetus behind this rule was to have a level playing field in a situation where now the generic manufacturers make most of the drugs that your constituents take. And that they have the same opportunity to react to the reports that they get of safety problems and rapidly modify the labels and bring them to FDA's attention. There are about 420 drugs right now that have no innovator on the market and so it will only be the generic manufacturers to whom those reports would come or to the FDA directly.

Mr. GINGREY. Under the proposed rule, I understand that generic innovator—now, innovator is the same as the brand——

Dr. WOODCOCK. Yes, sorry.

Mr. GINGREY [continuing]. The original drug that the company brought. I understand that generic and innovator companies could propose labeling changes through the CBE process and that the agency would post all of these suggested changes on your Web site on the FDA Web site before you would approve them. That is correct, isn't it?

Dr. WOODCOCK. Yes.

Mr. GINGREY. And for multi-sourced drugs, those that are the exact same, they are made by both the innovator and the generic companies, isn't it possible that each manufacturer could have different warnings posted for the same risk?

Dr. WOODCOCK. It is possible, but of course that would enable us to move very quickly. We get these now from innovators and they do a CBE–0 or we may hear from practitioners, we may have it reported to us, we may get it from the literature. We quickly evaluate those and we put out an FDA drug safety alert. I am sure you are familiar with these. Sometimes we say we are just looking at this issue. We don't know the answer yet.

Mr. GINGREY. Yes.

Dr. WOODCOCK. So we are an actor in this as well but we need to be made aware of what the manufacturers know.

Mr. GINGREY. Yes. Well, it seems like to me it would be confusing for doctors and patients, let's say, to go online, up-to-date WebMD, you pick it, and find different warnings and contraindications for the exact same drug. I don't see how that benefits public health when that happens.

Dr. WOODCOCK. Well, right now, of course there are drug safety controversies, as you know. And there is much on the blogosphere, on WebMD and everything else about different reported papers with this cardiovascular risk, this risk. Generally, FDA will put out a safety alert and say we are evaluating this issue. Here is what we know so far. Here is what we don't know. We will let you know when we have definitive information. When we do, then we would require all the manufacturers have the same label when we had——

Mr. GINGREY. Well, that is good news in my concluding 10 seconds because I was going to ask isn't it the FDA's job to referee these disputes and make class-wide labeling changes?

Dr. WOODCOCK. Yes, it is, and we do that. Yes.

Mr. GINGREY. Mr. Chairman, I yield back.

Mr. PITTS. The chair thanks the gentleman. That concludes the questions of the Health Subcommittee members who are here. I am sure they will have written questions that they will submit.

But at this time I would like to seek unanimous consent to permit the gentleman, Mr. Braley from Iowa, to ask questions. And without objection, so ordered.

The chair recognizes Mr. Braley 5 minutes for questions.

Mr. BRALEY. Thank you, Mr. Chairman. I really appreciate the Committee's indulgence in allowing me to be part of the hearing.

I want to follow up with a question, Dr. Woodcock, that Mr. Shimkus raised about input from physicians or physician groups.

Dr. WOODCOCK. Yes.

Mr. BRALEY. We heard from Mr. Waxman about the friend-of-the-court brief he filed in the Mensing case. Were you aware that the American Medical Association, the largest physician organization in the country, also filed a friend-of-the-court brief in that case?

Dr. WOODCOCK. No.

Mr. BRALEY. OK. Assume for the moment that they did and that one of the concerns they raised with the Supreme Court was the ethical dilemma that physicians face when they are confronted with inconsistent rules to protect their patients who receive brand name drugs——

Dr. WOODCOCK. Yes.

Mr. BRALEY [continuing]. As opposed to rules that protect their patients who purchase generic drugs.

Dr. WOODCOCK. Yes.

Mr. BRALEY. Is that the type of concern from healthcare providers that would be relevant to the agency in deciding whether or not to go forward with this rule?

Dr. WOODCOCK. Well, we just several weeks ago closed the comment period and we got over 100 comments, some of them fairly

voluminous, so I hope we have received input from a large number of sectors on this, including obviously the clinical community.

Mr. BRALEY. Mr. Lance raised concerns about similarly situated consumers being treated the same, but wouldn't that be an example raised by a physician group, the largest in the country, that would show how these different consumers of medications can be treated differently and that could raise concerns?

Dr. WOODCOCK. Well, I will say that certainly one of our issues is that the entities that are supplying medicine for a large number of patients in this country should stand behind their medicines.

Mr. BRALEY. One of the things that came up was Sentinel systems in your testimony, and this is a common word that is used in trying to promote patient safety throughout the healthcare delivery system, correct?

Dr. WOODCOCK. Yes.

Mr. BRALEY. In fact, the Joint Commission on Accreditation of Healthcare Organizations uses a Sentinel event system that requires any adverse event to be reported and then followed up so you get to the root cause of what caused the problem and develop an action plan to correct it. Are you familiar with that concept generally?

Dr. WOODCOCK. Yes, I am very familiar with it.

Mr. BRALEY. So, don't generic manufacturers of drugs have the same safety incentives as a matter of public health to warn consumers as brand name manufacturers?

Dr. WOODCOCK. Well, I would certainly hope so. They have the same regulatory requirements to be monitoring for the impact of their drug and to find out if any new safety event happened and to report it to the FDA.

Mr. BRALEY. And one of the concerns about this proposed rule that I would think conservatives would be very happy about is that it promotes personal responsibility and not shifting the burden to take care of patients to taxpayers through publicly funded healthcare systems. Isn't that true?

Dr. WOODCOCK. Not being a lawyer, it is difficult for me to comment on that.

Mr. BRALEY. If we don't have a remedy for people harmed by generic drugs and they have to go on Medicare and Medicaid, we end up paying for it as taxpayers, don't we?

Dr. WOODCOCK. That would apparently be the case sometimes.

Mr. WAXMAN. Would the gentleman yield to me?

Mr. BRALEY. I only have a few more minutes.

Mr. WAXMAN. I know. I wanted to take it.

Mr. BRALEY. One of the things that we know is there have been concerns raised about the cost of the proposed rule and we have heard testimony that 80 percent of the medications being dispensed are generics. The federal agency that is focused on promoting public health as part of the National Academy of Sciences is the Institute of Medicine——

Dr. WOODCOCK. Yes.

Mr. BRALEY [continuing]. And they have spent a lot of time studying this whole problem with preventable medical errors and especially medication errors. And this is a book they released in 2007 called Preventing Medication Errors.

Dr. WOODCOCK. Right.

Mr. BRALEY. And in here they write that in 2000, a study estimated that the cost of drug-related illnesses and deaths in the ambulatory setting in the United States was $177.4 billion.

Dr. WOODCOCK. Yes.

Mr. BRALEY. That is a lot of money.

Dr. WOODCOCK. Absolutely.

Mr. BRALEY. So if 80 percent of that marketplace is generic drugs and we would be talking about $140 billion cost associated with not reducing this problem and promoting patient safety. Isn't that true?

Dr. WOODCOCK. Well, I am very familiar with that book. I think that put in a lot of different safety problems together when they made those estimates. However, I would say that it is imperative that everyone monitor safety drugs in the outpatient and the ambulatory setting and that we improve our outcomes with patients.

Mr. BRALEY. Well, with my 5 seconds left I just want to mention Sophie Howe of Ames, Iowa, a young college student who was harmed by a generic drug and ended up having a lot of added cost associated with that, including payment of her student loans that were accelerated when she had to drop out of school because of her medical complications. And I think it is the human faces behind this problem that we should be thinking about.

Thank you.

Dr. WOODCOCK. Thank you.

Mr. BRALEY. I yield back.

Mr. PITTS. The chair thanks the gentleman. That concludes the questions.

At this time, we will have written questions that we will provide to you if you can please respond to those.

Thank you very much——

Dr. WOODCOCK. Thank you.

Mr. PITTS [continuing]. Dr. Woodcock, for your testimony and for your patience today.

Before I call the second panel, I ask unanimous consent to recognize the ranking member of the full committee, Mr. Waxman, for 5 minutes for a statement.

Mr. WAXMAN. Thank you very much, Mr. Chairman.

I know this is extraordinary to allow this but I am not going to be able to be here for the testimony of the next panel.

But I did want to comment on the fact that there is a disconnect at this hearing because people are talking about whether the label is going to be the same, how long it will take to be the same and whether the doctors are for this or not for it. I just want to point out what is really going on at this hearing.

The Supreme Court decision said that a generic drug manufacturer cannot be held liable under state law to warn people about the dangers of a drug that they manufacture that they know about because they can't put it in the label because under the law they cannot change their label unless the FDA changes the label for the brand and the generic company.

So in my brief to the Court I said, look, if they can't change their label, then they ought to be held liable under state law for the failure to let FDA know that there is a problem for which they ought

to give some notice to the public. It seems reasonable to me but the Court on a 5-to-4 basis said no. The only thing that would make them liable is if they failed to warn by a label change. And they can't make that label change, and therefore, the generic drug industry could open their champagne and drink to the success that they are never going to be held liable for. And that is great if you are never going to be held liable for them perhaps but it is not great for the consumers.

The FDA has looked at this issue and said, well, wait a minute. We have a requirement that brand name companies warn the consumer and they can even change their label, and then while we are considering whether or not we are going to impose that label requirement on everybody, they could go forward with it. But the generic drug companies can't do that.

Now, FDA is not looking at it from a legal liability. They are just looking at it from patient safety. It doesn't make sense that if a generic company discovers there is a problem, not to have them warn people, just as it is required by the brand name company. So they are changing the rules to be sure the consumer is protected, but in the process, it could and most likely would reverse the Supreme Court decision and make the generic companies liable for failure to warn people if they have the ability to warn them in a new label, just as the brand name companies have.

So while we are talking about all these other issues, we are missing what is really at stake here. We are going to hear that, I think, in this next panel because Mr. Neas and others are going to argue this is going to cost billions of dollars in liability that they hadn't had to worry about in the past. But I would submit that that doesn't make sense. Before the Supreme Court case, they were liable and they had to anticipate that, but they didn't have billions of dollars as a result of that vulnerability of liability. They were able to manage that reasonably well. And to expect, notwithstanding a report that we are going to hear about, which I very much doubt its validity, we are going to hear that, no, this is a big matter. This is going to be a huge liability for them.

Well, whether it will or will not, they should be held to the same standards in order to protect the public, and I hope they are liable if they do something wrong by not warning people in a label change. Because if they have information that their drug, as they learn now, could harm people, they ought to make that label change. Certainly, the brand name companies have to do it.

So I wanted this chance to make this statement now because I am not going to be able to be here to do it through questions.

I just must say, Mr. Neas, you have got a report. I just don't see it possibly being valid and it will be held up to some further questioning by this panel. But I can't see how it is valid. It seems to me highly inflated. It is like all the people that come in here and we want to regulate them, they say this will drive us out of business. And then when the regulations go into effect, they do it for a fraction of the cost. So I just think that people ought to put in perspective what this hearing is really all about.

And as I have now straightened everybody out about what is significant, I am going to leave you. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman.

Now, we will have our second panel. Please come to the witness table and I will introduce them in the order that they will speak.

On our second panel today we have Mr. Michael Shumsky, partner, Kirkland & Ellis; Mr. Ralph Neas, President and CEO of the Generic Pharmaceutical Association; and Ms. Allison Zieve, General Counsel, Public Citizen.

Thank you all for coming. Your written testimony will be made part of the record. You will each have 5 minutes to summarize your testimony.

And at this point the chair recognizes Mr. Shumsky, 5 minutes for his opening statement.

STATEMENTS OF MICHAEL D. SHUMSKY, PARTNER, KIRKLAND & ELLIS, LLP; RALPH G. NEAS, PRESIDENT AND CEO, GENERIC PHARMACEUTICAL ASSOCIATION; AND ALLISON M. ZIEVE, GENERAL COUNSEL, PUBLIC CITIZEN

STATEMENT OF MICHAEL D. SHUMSKY

Mr. SHUMSKY. Chairman Pitts, Ranking Member Pallone, and members of the subcommittee, thank you so much for inviting me to testify today. Though I filed administrative comments on these issues for a number of clients as part of my law practice, I would like to make clear at the outset that I am testifying today in my personal capacity and that the views I express are solely my own.

Over the past 30 years, the Hatch-Waxman Act has generated trillions of dollars in cost savings. And that phenomenal success stems from a simple but brilliant insight. Because two drugs with the same chemical and biological properties will have the same safety profile, FDA can safely approve generic versions of a previously approved drug without requiring new independent clinical trials

And it is precisely because two drug products with the same chemical and same biological properties will have the same safety profile that the statute naturally requires that generic drug labeling be "the same as the labeling approved for" that product's brand name equivalent. In a single word, sameness is both the statute's animating principle and the driving force of its success.

FDA now wants to permit generic drug warnings that are "inconsistent with the labeling for the RLD." That is the brand name equivalent. The agency has no power to do so. In our system of separated powers, the executive branch is bound by the laws this Congress passes. Indeed, as the Supreme Court explained the very same year Congress patched Hatch-Waxman, "if the intent of Congress is clear, that is the end of the matter for the agency must give effect to the unambiguously expressed intent of Congress." By this standard, FDA's proposal is indefensible. It pays no heed to Hatch-Waxman's plain language which explicitly requires generic labeling to be "the same as the labeling approved for" the brand name equivalent. And indeed, the statute further bars FDA from even approving a generic drug for sale in interstate commerce if its labeling is not "the same as" the approved labeling for the brand name drug.

The proposal also ignores FDA's lengthy track record on this issue. Indeed, FDA has repeatedly recognized the generic labeling

must be the same as the FDA-approved branded labeling at all times. It did so during the first Bush Administration, during the Clinton Administration, during the second Bush Administration and in its Supreme Court brief in the Mensing case earlier in this Administration.

And finally, FDA's proposal conflicts with the Supreme Court's recognition in both Mensing and in Bartlett that it is this Congress' statute, not merely FDA's regulations, that bars generics from using different warnings on their products. As the Court put the point very clearly in Bartlett, "Congress' decision to regulate the manufacture and sale of generic drugs in a way that reduces their cost to patients but leaves generic drug manufacturers incapable of modifying their warnings." In other words, Hatch-Waxman represents, as the Court said, "Congress' decision," not the FDA's.

I firmly believe that Hatch-Waxman's sameness requirement is supported by sound public policy and that FDA's rulemaking proposal threatens to harm the public health, but those issues are beyond the scope of my testimony today.

I also understand that the Court's recent decisions in this area are controversial, but as the Court recognized in Mensing and Bartlett, FDA has no power to adopt this proposal until this Congress changes Hatch-Waxman's core principle, the sameness requirement that has made that law one of the most successful pieces of legislation ever passed.

I have one minute left and I do want to highlight one thing and it was I think a very telling and very important exchange between Dr. Christensen on the one hand and Dr. Woodcock on the other. Dr. Christensen asked Dr. Woodcock about the origins of FDA's CBE proposal, and as she made clear, that proposal originated as an exercise in the FDA's view of enforcement discretion, meaning that the agency would not enforce the law as Congress wrote it. She then said, however, over time, FDA has changed its mind and now they interpret that to flow from the statute itself as opposed to the agency's disregard for the statute.

Let me translate that answer so that there is no mistaking what it was. FDA has ignored the law so long that the law has changed. That is a fundamental reordering of our Democratic process and a direct threat to the separation of powers. And I want to thank Chairman Pitts for holding this hearing so that we can explore those very important issues about the nature of our constitutional republic.

[The prepared statement of Mr. Shumsky follows:]

KIRKLAND & ELLIS LLP
AND AFFILIATED PARTNERSHIPS

655 Fifteenth Street N.W.
Washington D.C. 20005

Michael D. Shumsky
To Call Writer Directly:
(202) 879-5228
michael.shumsky@kirkland.com

(202) 879-5000

www.kirkland.com

Direct Facsimile:
(202) 654-9628

February 28, 2014

Hon. Joe Pitts
Chairman, Subcommittee on Health
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515
(202) 225-2927
(202) 225-1919 (facsimile)

Re: ***Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling: Hearing Before The Subcommittee On Health*** **(March 3, 2014)**

Chairman Pitts:

In connection with the above-noted hearing, please find attached to this letter a copy of the written remarks that I am submitting jointly with my law partner, Jay P. Lefkowitz, P.C. I look forward to appearing before the Subcommittee on Monday afternoon.

Respectfully submitted,

Michael D. Shumsky, Esq.

Prepared Remarks of
Michael D. Shumsky and Jay P. Lefkowitz, P.C.

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee:

Thank you for inviting us to testify in connection with this hearing.

Over the past thirty years, the Hatch-Waxman Act has generated literally trillions of dollars in cost savings. That success stems from a simple, but brilliant, insight: Because two drugs with *the same* chemical and biological properties will have *the same* safety profile, FDA can safely approve generic copies of an already approved drug without requiring new clinical trials. And precisely *because* two drug products with *the same* chemical and biological properties will have *the same* safety profile, the statute naturally requires that generic drug labeling be "*the same as* the labeling *approved* for the" product's brand-name equivalent (or "RLD"). 21 U.S.C. § 355(j)(2)(A)(v) (emphasis added); *see also id.* § 355(j)(4)(G). In a word, *sameness* is the statute's core principle and the driving force of its success.

FDA now wants to permit generic drug warnings that are "*inconsistent* with the labeling for the RLD." FDA, *Proposed Rule: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products*, 78 Fed. Reg. 67985, 67986 (Nov. 13, 2013) (emphasis added). The Agency has no

power to do so. In our system of separated powers, the Executive Branch and Judiciary are bound by the laws Congress passes. Indeed, as the Supreme Court explained the same year Congress passed Hatch-Waxman, "If the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Chevron USA, Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 842-43 (1984).

By this standard, FDA's proposal is indefensible. It pays no heed to Hatch-Waxman's plain text, which explicitly requires generic labeling to be "the same as the labeling" FDA previously "approved for the" generic drug's brand-name equivalent, and indeed bars FDA from approving a generic drug if its labeling is *not* "the same as" the approved labeling for the brand-name drug. 21 U.S.C. §§ 355(j)(2)(A)(v) & 355(j)(4)(G).

The proposal also ignores FDA's own record on this issue. Indeed, FDA has recognized during every Administration in recent memory that generic labeling must be the same as the FDA-approved branded labeling. It did so during the first Bush Administration, *Final Rule: Abbreviated New Drug Regulations*, 57 Fed. Reg. 17950 (April 28, 1992); during the Clinton Administration, *Proposed Rule:*

Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels, 65 Fed. Reg. 81082 (Dec. 22, 2000); during the second Bush Administration, *Final Rule: Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 Fed. Reg. 3922 (Jan. 24, 2006); and even earlier in this Administration, Br. for the United States as *Amicus Curiae*, *PLIVA, Inc. v. Mensing*, 131 S.Ct. 2567 (filed Mar. 2, 2011).

FDA's rulemaking proposal defies what Representative Waxman himself has said about this issue. In his words, "*it is clear that a generic and a brand-name label must be the same and that a generic firm cannot unilaterally change its label.* To permit individual generic drug labels to differ significantly from their brand-name counterparts—particularly with respect to safety information—would thwart the 'sameness' goal reflected in the Hatch-Waxman Amendments." Br. of Rep. Henry A. Waxman as *Amicus Curiae*, *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2576, at 14 (filed Mar. 2, 2011) (emphasis added).

And FDA's proposal conflicts with the Supreme Court's recognition that the statute itself—not merely the FDA regulations—bars generics from presenting

different warnings. As the Court explained in *Bartlett*, Hatch-Waxman embodies "*Congress' decision* to regulate the manufacture and sale of generic drugs in a way that reduces their cost to patients but leaves generic drug manufacturers incapable of modifying either the drugs' compositions or their warnings." *Mutual Pharm. Co. v. Bartlett*, 133 S. Ct 2466, 2480 (2013) (emphasis added).

We firmly believe that Hatch-Waxman's sameness requirement is supported by sound public policy and that FDA's rulemaking proposal threatens to harm to the public health, though those issues are beyond the scope of our testimony today. We also understand that the Supreme Court's recent decisions in this area are controversial. But as the Court recognized in both *Mensing* and *Bartlett*, it is up to this body—not FDA—to change the law if it believes change is warranted.

Respectfully submitted,

Michael D. Shumsky, Esq.
Jay P. Lefkowitz, P.C.

Mr. PITTS. The chair thanks the gentleman and recognizes the gentleman, Mr. Neas, 5 minutes for an opening statement.

STATEMENT OF RALPH G. NEAS

Mr. NEAS. Good afternoon, Chairman Pitts, Ranking Member Pallone, and members of the subcommittee. Thank you for inviting me to testify on the FDA's proposed changes to generic drug labeling. I am Ralph G. Neas, President and CEO of the Generic Pharmaceutical Association.

This year we commemorate the 30th anniversary of the Hatch-Waxman Act, which by any measure has been one of our most effective laws ever passed. This remarkable law initially projected to save maybe a few million dollars a year has saved the U.S. healthcare system more than $1.2 trillion over the past decade, $217 billion in 2012 alone.

The quality and affordability of generic medicines is vital to public health and the sustainability of the healthcare system. The very heart and soul of the Hatch-Waxman Act is the sameness principle under which generic manufacturers must prove to the FDA that their version of a drug contains the same active ingredient as the brand product, is identical in strength, dosage form, and route of administration, and importantly for today's discussion, has the same labeling. These requirements give consumers, doctors, and pharmacists confidence in the safety and effectiveness of generic medicines.

The top priority for generic manufacturers is assuring patient safety for the hundreds of millions of people who rely on our products to live healthier and longer lives. The company's proactively participate with FDA to ensure the timeliness, accuracy, and completeness of drug safety labeling in accordance with all current regulations. These manufacturers report all serious and unexpected adverse events to the FDA within 15 days. All others report it quarterly or annually. The generic industry takes these responsibilities seriously.

Unfortunately, the FDA's proposed rule would substantially undermine the enormously successful Hatch-Waxman Act and put both patient safety and healthcare savings at risk by directing generic manufacturers to make unilateral labeling changes without prior FDA approval. The rule creates a system whereby multiple different labels, including different warnings, can simultaneously exist in the marketplace for the same drug with the same active ingredient.

Generic manufacturers only have access to the scientific and medical evidence for their individual products representing a fraction of the total market. They do not have access to the clinical trial data and other proprietary information of the brand manufacturer or current information and data from other generic manufacturers. Only the FDA has access to all the data and information. A generic manufacturer that unilaterally changes its label therefore does so with incomplete information.

It is difficult to overstate the negative implications of the proposed rule on patient safety and on consumer access to affordable medicines. Allowing for multiple different drug labels in the market for the same product would upend 30 years of law and regulation

and create substantial confusion for everyone in the healthcare system. Uniform safety information provides certainty for patients and providers that they can rely on consistent information and inform their decisions in medical conversations.

Identical labels also underscore the critical point that once generic medicines are approved by the FDA, they are proven scientifically equal to the brand medicine in terms of safety, efficacy, and quality. The risk of over-warning and the flood of unnecessary labeling changes is substantial. Multiple versions of critical safety information would inaccurately imply therapeutic differences between the generic drug and brand drug that do not exist. The exaggeration of risk and inclusion of unsubstantiated warnings will cause provider confusion and discourage the use of beneficial treatments.

In addition to seriously jeopardizing patient safety, the proposed rule would also burden consumers, businesses, and state and federal governments with billions of dollars in increased prescription drug costs. A recent economic analysis found that the proposed rule would conservatively add $4 billion annually to the Nation's already high healthcare cost, including $1.5 billion in Medicare and other government programs.

It should be no surprise that 19 organizations representing those populations that most rely on access to affordable generic drugs and representatives from virtually every sector of the pharmaceutical supply chain, most importantly pharmacists and pharmacy organizations representing more than 100,000 pharmacists and 45,000 pharmacies, have submitted letters to the FDA raising their significant concerns that the proposed rule could jeopardize patient access and patient safety.

Unfortunately, neither the FDA nor the Office of Management and Budget conducted a robust cost-benefit analysis as OMB is required to do to examine the economic implications of this rule in increased healthcare costs.

I am here today with a simple message. We can do better. GPhA fully supports a streamlined, efficient, and transparent process for timely submission in updating their safety information for generic drugs for healthcare providers and the public. A key element of any new system must include timely FDA review of all available clinical data and safety signals, including the nonpublic data of the NDA holder.

Underlying this process should be one bedrock principle: Generic drug labels must be FDA-approved; it must be based on scientific evidence. Such a system would advance our shared goals of protecting the public health and improving patient safety. Congress should ensure that the FDA has sufficient resources to do so. We would welcome the opportunity to work with others in the healthcare system in a multi-stakeholder collaboration on this matter. The FDA should hear from patient advocates, pharmacists, physicians, payers, not just trial lawyers, and others in the supply chain who could offer expertise, experience, and perspective.

The sustainability of our healthcare system depends on the continued access to affordable generic medicines. We will work hard to make sure that any changes to labeling rules and regulations

protect patient safety, align with federal law, and do not hinder patient access to more affordable generic medicines.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Neas follows:]

GPhA
Generic Pharmaceutical Association

TESTIMONY OF RALPH G. NEAS

PRESIDENT AND CEO

THE GENERIC PHARMACEUTICAL ASSOCIATION

"EXAMINING CONCERNS REGARDING FDA'S PROPOSED CHANGES TO GENERIC DRUG LABELING"

BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

APRIL 1, 2014

777 6th Street, NW • Suite 510 • Washington, DC 20001 • p: 202.249.7100 • f: 202.249.7106 • www.gphaonline.org

Good morning Chairman Pitts, Ranking Member Pallone, and Members of Subcommittee. Thank you for inviting me to testify before the Subcommittee on the FDA's proposed changes to generic drug labeling.

I am Ralph G. Neas, President and CEO of the Generic Pharmaceutical Association (GPhA). GPhA represents the manufacturers and distributors of finished generic pharmaceuticals, manufacturers and distributors of bulk pharmaceutical chemicals, and suppliers of other goods and services to the generic industry.

Introduction

This year, we commemorate the 30th anniversary of the Hatch-Waxman Act, the bipartisan compromised signed into law by President Ronald Reagan on September 24, 1984. By any measure – and by every measure -- Hatch-Waxman is one of our nation's most effective laws.

The law struck a delicate balance between fostering competition and rewarding innovation and very quickly produced results. During the 22 years preceding Hatch-Waxman, only 15 generics had been formally approved by the FDA. But within one year after Hatch-Waxman became law, more than ***one thousand*** generic applications were submitted to the FDA.

Patients soon began reaping the benefits of the new law as hundreds of FDA-approved safe, effective and lower cost versions of prescription drugs made their way to pharmacies, health care centers, hospitals, and long-term care facilities.

Insurers and other third-party payers, including federal and state governments, also became beneficiaries of Hatch-Waxman, as the savings generated by generic medicines began adding up.

This remarkable law, initially projected to save maybe a few ***million*** dollars a year has saved U.S. consumers, patients and the health care system more than $1.2 trillion over the past decade — $217 billion in 2012 alone — which equates to $4 billion in savings every week. Generic pharmaceuticals fill 84 percent of the prescriptions dispensed in the U.S. but consume just 27 percent of the total drug spending.

The quality and affordability of generic medicines is vital to public health and the sustainability of the health care system, and the top priority for GPhA and generic manufacturers is protecting patient safety and assuring access to affordable medicines.

Generic drug companies proactively participate with the FDA in ensuring the timeliness, accuracy, and completeness of drug safety labeling in accordance with all current regulatory requirements. Most recently, the generic industry has demonstrated its commitment to patient safety through its support of the historic Generic Drug User Fee Act and last year's Drug Quality and Security Act.

Through both of these laws, which this Committee crafted on a bipartisan basis, the generic industry has demonstrated its commitment to assuring the quality of the prescription drug supply and promoting the public health, while also assuring patient access to affordable medicines. GPhA and our member companies are committed to assuring patient safety for the hundreds of millions of people who rely on our products to live healthier and longer lives.

Unfortunately, the FDA's recently proposed rule on prescription drug labeling would have the opposite effect. It would completely undermine the enormously successful Hatch-Waxman Act, and put both patient safety and health care savings at risk.

Disappointingly, the FDA's proposal as drafted would create substantial confusion for pharmacists, doctors, nurses, patients and others in the health care system by allowing for multiple, different drug labels in the market for the very same product, upending 30 years of law and regulation. This would not only jeopardize patient safety, but as a recent economic study has shown, would also 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.

All of this is antithetical to the basic purposes of Hatch-Waxman and would jeopardize its continued viability.

Hatch-Waxman Act and Sameness

The Hatch-Waxman Act permitted generic drug manufacturers to rely on findings of safety and efficacy for a brand drug as support for approval of the generic drug application, provided the proposed generic product was the "same as" the reference product upon which it is based. In order to ensure that generic drug manufacturers could enter the market to produce drugs less expensively, and not subject patients to unnecessary testing, Congress expressly exempted them from the expensive, time-consuming, and ultimately repetitive clinical testing and trials that already had been performed on the innovator drug. In turn, the brand-name drug industry was awarded additional product protection in the form of market exclusivity, patent term extensions, and patent protections.

Under this "sameness" requirement, generic pharmaceutical manufacturers must prove to the FDA that their version of a drug provides the same safety and efficacy as the brand product; contains the same active ingredient; is identical in strength, dosage form, and route of administration; and, importantly for today's discussion, has the same labeling. Doctors, patients, and pharmacists can all have confidence in the safety and effectiveness of generic medicines.

Under the statute and regulations governing Abbreviated New Drug Application (ANDA) submission and approval, a generic drug product is required to maintain the same labeling as the Reference Listed Drug (RLD) after ANDA approval, with limited exceptions. As has been the case since the passage of the Hatch-Waxman Act, only the innovator company, and not a generic drug manufacturer, can add to or strengthen a warning without first obtaining FDA's approval.

Likewise, FDA can initiate labeling changes, including addition of warnings, if the Agency determines they are warranted on the basis of new information received after NDA approval. If the innovator company has received approval for a change in labeling, the Office of Generic Drugs (OGD) allows the generic manufacturer to revise its label to comply with the exact change approved for the innovator. The FDA's regulations implementing the Hatch-Waxman Act correctly explained that consistency between labeling of the brand and generic drug not only is required by the statute, but also is essential to avoid confusion in the marketplace.

In accordance with Hatch-Waxman, FDA has long maintained the position that labeling changes cannot be made unilaterally by a generic manufacturer. In fact, FDA had affirmed this requirement as recently as July 2013 in a guidance related to brand drug labeling changes ("Guidance for Industry" Safety Labeling Changes - Section 505(o)(4) of the FD&C Act").

Recently, the Supreme Court decisions *PLIVA, Inc. v. Mensing* and *Mutual Pharm. Co., Inc. v. Bartlett* acknowledged the clarity and unambiguity of the statutory language that requires a generic drug's label to be the same as that of its RLD and that prevents generic drug manufacturers from changing their labeling to include additional or strengthened warnings. The decision in *PLIVA v. Mensing* outlined the Court's understanding that the Federal Food Drug and Cosmetic Act (FFDCA) requires "the warning labels of a brand-name drug and its generic copy must always be the same – thus, generic drug manufacturers have an ongoing federal duty of sameness."

FDA's Proposed Rule

On November 13, 2013, the FDA issued a proposed rule regarding Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products. FDA made it clear that it intends to establish "parity" between ANDA and New Drug Application (NDA) sponsors by requiring ANDA sponsors to submit Changes Being Effected supplements (CBE-0) to modify their labeling when they receive or otherwise obtain new safety-related information. The labeling changes are expected even though they will result in the generic drug labeling differing from the RLD labeling.

It is difficult to overstate the negative implications of the Proposed Rule on the generic pharmaceutical industry and on patient safety. The Proposed Rule creates a regulatory framework whereby multiple, different labels, including

different warnings, can simultaneously exist in the marketplace for the same drug with the same active ingredient. GPhA and our member companies are strongly concerned that the FDA's proposed rule strikes at the very heart of the "sameness principle" that is fundamental to the Hatch-Waxman Act.

Generic manufacturers only have access to the scientific and medical evidence for their individual products, representing a fraction of the total market. They do not readily have access to the clinical trial data and evidence of the brand manufacturer or current information and data from other generic manufacturers; only the FDA has access to all data and information, as that information is proprietary. A generic manufacturer that unilaterally changes its label therefore does so with limited, incomplete information. Such a labeling change may actually do more harm than good since it would disregard years of the brand company's scientific and medical history on the product. Since the FDA is the only entity that has access to all the information and has the expertise to evaluate and address this information, it is the only body in a position to decide whether a labeling change is warranted.

Adverse Event Reporting

After approval, generic manufacturers still have extensive obligations under federal law to ensure that their products are safe and properly manufactured. Generic manufacturers develop written procedures to closely monitor their products and for reporting of adverse events. All adverse events must be reported to the FDA. Serious and unexpected events are reported within 15 days,

and all others are reported quarterly or annually. Generic manufacturers also must submit annual reports that address safety and effectiveness issues for their products. The generic industry takes these pharmacovigilance requirements very seriously and is committed to assuring that FDA receives all adverse event information in a timely manner.

In its rulemaking, the Agency states that the recent *Mensing* decision alters the incentives for generic manufacturers to comply with these requirements for robust postmarketing surveillance, adverse event reporting, and ensuring the accuracy of product labeling. This is simply untrue. A generic manufacturer has exactly the same reporting and surveillance obligations now as it did prior to the Supreme Court decision. Moreover, there is no evidence that generic drug manufacturers do not comply with their existing post-marketing obligations or that they do not compile and submit the periodic reports.

Some proponents of the rule change have argued that since the marketplace has changed since the passage of Hatch-Waxman and generics now make up a majority of all prescription drugs dispensed in the U.S., a generic manufacturer will now somehow have more complete information about the complete adverse event profile for a single product. This reasoning is severely flawed. Grouping the total market share of all generic drug manufacturers for a particular drug ignores the reality of the marketplace. While one generic drug manufacturer may have a larger share of the market than another generic drug manufacturer, no

manufacturer has ready access to all the adverse event data; and therefore, cannot make a totally informed decision.

Provider Confusion

Uniform safety information provides certainty for patients, doctors, pharmacists and nurses and assures all healthcare 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 proven scientifically equal to the brand medicine in terms of safety, efficacy and quality.

By creating a framework under which one drug could have multiple different warning labels, the proposed rule would compromise patient safety. GPhA is very concerned that multiple versions of critical safety information would lead to unnecessary confusion and uncertainty for prescribers and other healthcare professionals, with harmful consequences for patients. A unilateral change by one generic manufacturer to the warnings section of its label could inaccurately imply therapeutic differences between the generic drug and the brand drug that do not exist, and therefore could be misleading to healthcare professionals and consumers. The danger of negative effects for patients, including a reduction in adherence to their doctor's prescribed regime, is very real.

Requiring generic manufacturers to make unilateral changes, based on incomplete information, will lead to a flood of unnecessary labeling changes. The exaggeration of

risk and inclusion of unsubstantiated warnings will cause provider confusion and discourage the use of beneficial treatments.

Economic Impact

Flooding the marketplace with multiple versions of labels for the same medicines would not only seriously jeopardize patient safety, but also would burden consumers, taxpayers, large and small businesses, and state and federal governments with billions of dollars in increased costs for generic medicines. A recent analysis by economic consulting firm Matrix Global Advisors found that the proposed prescription drug labeling rule would add $4 billion dollars annually to the nation's already high health care costs. Of the projected increase in health care costs, the analysis estimates that Medicare and other government programs will incur $1.5 billion in annual new spending, while private insurers and patients will pay $2.5 billion per year.

The proposed rule would expose generic drug manufacturers to substantial new tort liability costs, which in turn would require them to adjust prices to stay in business, withdraw products, or decline to launch new affordable versions of brand medicines. Increased liability would also accrue to pharmacists, physicians and other participants in the health care system, beyond the substantial confusion for all stakeholders, impeding health care decisions and delivery.

The result would be fewer generic drugs coming to market and manufacturers withdrawing from certain high-risk markets, leading to drug shortages, the underutilization of affordable generics medicines, and ultimately increased prescription drug spending.

Unfortunately, neither the FDA nor the Office of Management and Budget (OMB) conducted a robust cost-benefit analysis – as OMB is required to do – to examine any of these potential pitfalls and increased costs. The FDA overlooked the proposed rule's very real financial impact on the affordability and availability of generic medications for patients and all stakeholders in the drug supply chain.

Public Health

Since the passage of the Hatch-Waxman Act, generic manufacturers have fulfilled important pharmacovigilance responsibilities to protect the patients they serve. GPhA fully supports a streamlined, efficient, and transparent process for timely submission and updating of safety information regarding pharmaceutical products for health care practitioners and the general public. We would support a process in which generic firms would actively assist FDA in its determination that a change to labeling is warranted based upon new safety information and in an efficient and prompt review of proposed changes by FDA. A key element of any new system must include timely FDA review of all available clinical data and safety signals, including the proprietary, non-public data of the NDA holder.

Such a system would advance our shared goals of protecting the public health and improving patient safety.

Many proponents of the rule change cite a desire to address the federal preemption of state failure-to-warn claims against generic manufacturers affirmed by *Mensing*. In our view, as a federal public health agency, the FDA should focus on assuring patient safety, and not on state tort liability claims.

Conclusion

The sustainability of our health care system, indeed our national economy, depends on the continued access to safe, effective, more affordable generic medicines in a timely manner as envisioned under Hatch-Waxman. 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 all of these goals.

While GPhA strongly opposes the FDA's Proposed Rule on Labeling, we would welcome the opportunity to work with others in the health care system, in a multi-stakeholder collaboration, to assist the FDA in strengthening the current labeling regulations. Inclusiveness has to be the operating principle. The FDA should hear from pharmacists, physicians, patient advocates, payors, and others in the pharmaceutical supply chain who could offer expertise, experience, and perspective.

The generic pharmaceutical industry will continue to work with the Congress, FDA, and other stakeholders to make sure that any changes to labeling rules and regulations protect patient safety, align with federal laws, and do not hinder patient access to more affordable generic medicines.

Thank you, Mr. Chairman, and I would be happy to answer any questions you may have.

SUMMARY OF TESTIMONY OF RALPH G. NEAS, PRESIDENT AND CEO OF
THE GENERIC PHARMACEUTICAL ASSOCIATION
BEFORE THE ENERGY AND COMMERCE SUBCOMMITTEE ON HEALTH
U.S. HOUSE OF REPRESENTATIVES – APRIL 1, 2014
"EXAMINING CONCERNS REGARDING FDA'S PROPOSED CHANGES TO GENERIC DRUG LABELING"

GPhA is the nation's leading trade association for the generic drug industry. Generic pharmaceuticals fill 84 percent of the prescriptions dispensed in the U.S. but consume just 27 percent of the total drug spending, and the use of generic drugs has saved U.S. consumers and the health care system $1.2 trillion over the past decade.

Patient Safety: The top priority for generic manufacturers is protecting patient safety and assuring access to affordable medicines. Generic drugmakers proactively participate with FDA to ensure the timeliness, accuracy, and completeness of drug safety labeling in accordance with all current regulatory requirements. We are committed to assuring patient safety for the hundreds of millions of people who rely on our products.

Hatch-Waxman Act of 1984: The Act has been enormously successful. Under its "sameness" requirement, generic manufacturers must prove to FDA that a generic provides the same safety and efficacy as the brand; contains the same active ingredient; is identical in strength, dosage form, and route of administration; and has the same labeling. These requirements give patients and providers confidence in the safety and effectiveness of generic medicines.

Adverse Event Reporting: Generic manufacturers have extensive post-approval obligations to ensure that products are safe and properly manufactured. All serious and unexpected adverse events are reported within 15 days, and all others are reported quarterly or annually, in addition to annual reports on the safety and effectiveness of products.

FDA's Proposed Rule: GPhA is strongly concerned that the FDA's proposed rule strikes at the very heart of the "sameness principle" that is fundamental to the Hatch-Waxman Act. It creates a regulatory framework whereby multiple, different labels, including different warnings, can simultaneously exist in for the same drug with the same active ingredient. Generic manufacturers, who only have access to the data for their individual products and do not have access to the brand clinical trial data, should not make unilateral label changes. The FDA, the only entity with access to all the information, should make these labeling decisions.

Provider Confusion: Uniform safety information provides certainty for patients, doctors, pharmacists and nurses and assures that they can rely on consistent information to inform their decisions. The proposed rule would create substantial confusion for providers by allowing for multiple, different drug labels for the same product

Public Health: A unilateral change by one generic manufacturer to a product's label would inaccurately imply therapeutic differences between the generic and brand drug that do not exist. The exaggeration of risk and inclusion of unsubstantiated warnings will cause confusion for providers and consumers and discourage the use of treatments.

Economic Impact: The rule would not only jeopardize patient safety, but as a recent economic study has shown, would also create billions of dollars in annual increased costs for consumers, taxpayers, businesses, and state and federal governments: $4 billion annually. The rule would decrease patient access, impede health care decisions and delivery, make fewer generic drugs available, and lead to shortages of critical generic drugs.

Conclusion: GPhA fully supports a streamlined, efficient, and transparent process for timely submission and updating of safety information for generic drugs for health care practitioners and the public. We would support a process in which generic firms would actively assist FDA in its determination that a change to labeling is warranted based upon new safety information and in an efficient and prompt review of proposed changes by FDA. A key element of any new system must include timely FDA review of all available clinical data and safety signals, including the proprietary, non-public data of the NDA holder. Generic manufacturers should not make labeling changes unilaterally. We would welcome the opportunity to work with others in the health care system, in a multi-stakeholder collaboration, to assist the FDA in strengthening the current labeling regulations.

Mr. PITTS. The chair thanks the gentleman and now recognizes Ms. Zieve 5 minutes for an opening statement.

STATEMENT OF ALLISON M. ZIEVE

Ms. ZIEVE. Thank you, Mr. Chairman.

I am general counsel of Public Citizen and director of Public Citizen Litigation Group. Our office submitted the citizen petition that the FDA granted in part by issuing the proposed rule that we are discussing today.

Since 1984, despite considerable changes in the market, FDA regulation of generic labeling has remained substantially unchanged. Since 1985, at the request of Pharma and other specific brand name manufacturers, the FDA has allowed the brands to make safety-related labeling changes without prior approval. The concerns that motivated the FDA to adopt these changes being affected or CBE option 30 years ago—the need to promptly inform patients and physicians and the interest and efficiency and resource management—apply equally today.

FDA continues to lack the resources to be the primary instigator of post-approval labeling changes and cannot timely pre-approve every safety update. Therefore, today, with generics comprising such a large percentage of all prescriptions filled, to fulfill the goal of timely labeling updates to physicians and patients, the CBE process must be available to generic manufacturers as well.

The majority of labeling changes are initiated by manufacturers, not by the FDA, and based on publicly available adverse event reports and medical literature. The brand name manufacturer drops to a small percentage of the market very quickly after generics enter the market and often stop selling the drug altogether. More than 400 unique drugs fall into this category. In these instances, if generic manufacturers are not actively monitoring and proposing safety updates, no manufacturer is doing so at all. But at the same time, it is undisputed that critical safety information may come to light after entry of the generic onto the market and after exit of the brand-name product.

The concern that the proposal will result in confusing or inconsistent labeling is unwarranted, I think, based on unfounded worst-case scenarios and belied by current practice. For the past 30 years brand labeling has been different from generic for months, or as Dr. Woodcock testified, up to a year even in some cases after the brand updates the labeling. We have seen no evidence of confusion.

And despite this sameness concern of Hatch-Waxman, variations of labeling are built into current regulations and have been for 30 years such as the listing of different formulations or a different indication. Sameness has never been a literal requirement of the law.

Yet again, physicians and pharmacists have not complained of confusion. In fact, the National Physicians Alliance submitted a comment to the FDA 2 weeks ago saying that confusion is not their concern. Their concern is updated safety information.

Finally, the manufacturers have argued, and I think this is the real objection, that the proposed rule, if finalized, will expose them to liability for failure to warn. They argue that the proposed rule will increase the cost of generic drugs and insurers may refuse to insure them and that some manufacturers may even decline to

enter the market. But both recent history and current reality prove these theories wrong. Until 2011, generic drug manufacturers faced the same liability risk that they would under the revised rule because until the Court's decision in Pliva v. Mensing, generic companies could be and sometimes were sued for failure to warn and many cases were resolved favorably to the patient. Even today, some lawsuits, although far fewer, are brought in cases where the generic has failed to make a required update. So the proposal would not create a new cost but one borne and managed very well by the industry until just 30 years ago and still borne fully today by brand name manufacturers.

It is important to keep in mind—I think this has gotten lost today—that lawsuits for failure to warn, when meritorious, occur because a patient suffered injury due to the lack of an adequate warning. Thus, the many lawsuits about metoclopramide, for example, people took a drug for reflux and developed the neurological disease tardive dyskinesia, which is often permanent. Adverse event reports and studies documented this problem for years but the brand name company did not revise the labeling and the generics said nothing.

Of course, the manufacturer is not responsible every time a patient is injured but sometimes the manufacturers, including generic manufacturers, turn a blind eye and the current system allows the generic manufacturers to do this. The result is more injury and more cost because immunizing a company from liability does not make the patient's costs go away. They are carried by the patients, the health insurance, and taxpayers. For this reason, by giving generic manufacturers the tools and incentives to update safety labeling, the proposed rule will be to a cost savings, savings in medical care for the patients who will not be injured because they and their physicians are armed with updated information about safety risks.

Thank you.

[The prepared statement of Ms. Zieve follows:]

1600 20th Street, NW • Washington, D.C. 20009 • 202/588-1000 • www.citizen.org

TESTIMONY OF ALLISON M. ZIEVE

Director of Public Citizen Litigation Group

and

General Counsel of Public Citizen

BEFORE THE COMMITTEE ON ENERGY AND COMMERCE

SUBCOMMITTEE ON HEALTH

UNITED STATES HOUSE OF REPRESENTATIVES

HEARING ON

EXAMINING CONCERNS REGARDING FDA'S PROPOSED CHANGES

TO GENERIC DRUG LABELING

April 1, 2014

Mr. Chairman and Members of the Committee, thank you for inviting me to share with you my views on the Food and Drug Administration's proposed rule addressing supplemental applications proposing labeling changes for approved drugs. I am Director of Public Citizen Litigation Group and General Counsel of Public Citizen, and my work involves both regulatory matters such as FDA regulation and access to courts issues, such as federal preemption of state-law claims. In August 2011, Public Citizen submitted to the FDA a citizen petition asking the agency to authorize generic drug manufacturers to revise product labeling through the procedures available to brand-name manufacturers. In November 2013, the FDA granted the citizen petition in part by issuing the proposed rule.[1]

I am here to speak in strong support of the FDA's proposal, which will bring post-market regulation of generic drugs in line with the realities of the pharmaceutical market today and help ensure that drug labeling provides adequate warnings to patients based on information that comes to light after the drug is on the market. While the objections to the proposal focus on liability, the purpose of the rule is to improve drug safety.

Since 1984, the prescription-drug market has transformed: Sales of generic drugs have skyrocketed and now constitute the vast majority of all prescriptions filled. Yet despite considerable changes in the market, FDA regulation of generic labeling has remained substantially unchanged.

Until 1985, the FDA generally required prior approval for all labeling changes.[2] Brand-name manufacturers argued to the FDA that this requirement was unnecessary, took FDA reviewers away from other important work, and caused costly delays. In response, the FDA identified numerous types of changes that manufacturers could make without prior approval, including "[c]hanges that add or strengthen a contraindication, warning, precaution, or statement about an adverse reaction, drug abuse, dependence, or overdosage, or any other instruction about dosage and administration that is intended to improve the safe use of the product."[3] These changes, the FDA said, "would help concentrate the agency's limited resources more on applications for marketing, and would also permit pharmaceutical manufacturers to institute certain postmarketing changes sooner,"[4] thereby advancing safety.

The concerns that motivated the FDA to adopt the CBE option nearly 30 years ago—the need to promptly inform physicians and patients, and the interest in efficiency and resource management—apply equally here. As was true then, the agency lacks the resources to be the

---

[1] A copy of the citizen petition is available at http://www.citizen.org/documents/Citizen-Petition-8-26.pdf. This testimony is based on the March 13, 2014, comments of Public Citizen in support of the proposed rule and available at http://www.citizen.org/documents/Comments%20on%20NPRM%203-12-14.pdf.

[2] *See* 47 Fed. Reg. 46622, 46634 (1982).

[3] *Id.* at 46635.

[4] *Id.*

primary instigator of post-approval labeling changes and cannot quickly pre-approve safety updates to the labeling of every approved drug. And as was true then, safety information often comes to light or is clarified after initial approval.

What is different now is that generic drugs comprise such a large percentage of all prescriptions filled and such an overwhelming percentage of all prescriptions filled for off-patent drugs. Therefore, today, to fulfill the goal of providing timely labeling updates to physicians and patients, the CBE process must be available to generic, as well as to brand-name, manufacturers. As generic market share increases, the brand-name manufacturer loses incentive to devote resources to post-approval safety monitoring. 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.

Last summer, Public Citizen compiled a list of drugs for which black-box warnings—reserved for the most serious warnings—were added after a generic equivalent entered the market. Restricting our research to a five-year period, we identified 53 drugs for which a black-box warning calling attention to serious or life-threatening risks was added after generic market entry—and the list is likely incomplete. The data show that new safety issues of the most serious type commonly arise after generics have entered the market, and they underscore the public health imperative of maintaining an incentive for generic manufacturer surveillance for safety.[5] A 2013 article authored jointly by three FDA staff and two academics confirms this result: "The most critical safety-related label changes, boxed warnings and contraindications, occurred a median 10 and 13 years after drug approval (and the range spanned from 2 to 63 years after approval), underscoring the importance of persistent and vigilant postmarket drug safety surveillance."[6]

This point is particularly important because brand-name manufacturers not only drop to a small market share fairly quickly after introduction of a generic onto the market, but the brand-name manufacturer often stops selling the drug altogether.[7] The FDA recently estimated the number of generic drugs with unique active ingredients for which the brand-name drug is no longer marketed as approximately 420.[8] And a 2012 study by the Generic Pharmaceutical Association notes that, for 45 percent of generics sold, no branded product is

---

[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* 7-10 (2013), available at http://www.citizen.org/documents/2138.pdf. The report is also attached as an exhibit to this testimony.

[6] Jean Lester, et al., *Evaluation of FDA safety-related drug label changes in 2010*, 22 Pharmacoepidemiology and Drug Safety 302, 304 (2013).

[7] *See* Public Citizen, *supra* note 5, at 12-23.

[8] FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products, Preliminary Regulatory Impact Analysis* at 9 (2013) (FDA Regulatory Impact Analysis).

currently on the market.[9] In these instances, if generic manufacturers are not actively monitoring and proposing safety updates, no manufacturer is doing so at all.

Our research and the medical literature confirm the findings of a 2010 FDA study that "critical safety-related label changes" may occur many years *after* approval, *after* entry of the generic onto the market, and *after* exit of the brand-name product.[10]

It is no answer to say that the FDA does postmarketing surveillance and can order labeling changes. The premise of the postmarketing regulatory scheme is that the FDA does not and cannot take primary responsibility for monitoring the thousands of drugs on the market. As the Supreme Court put it, since the Food, Drug, and Cosmetic Act was enacted, "[i]t has remained a central premise of federal drug regulation that the manufacturer bears responsibility for its label at all times."[11] This point is borne out in practice: In 2010, manufacturers "initiated 58% of safety-related label changes compared to 42% initiated by the FDA." Although the "FDA initiated most of the boxed warnings (84% versus 16%)," manufacturers initiated 78% of the changes to the adverse reaction section.[12] By giving generic manufacturers more responsibility for labeling, the proposed rule encourages more vigilance, both to monitor adverse events and medical literature to determine when labeling updates are called for and also to monitor the FDA's labeling webpage for approved (and required) updates for the drug. Importantly, FDA regulations have long required generic manufacturers to do this monitoring (the same as brand-name companies).

Generic manufacturers are fully capable of initiating labeling changes. Mechanically, the procedure already exists, as the CBE process is well-established, and generic manufacturers already have in place procedures for revising labeling in response to FDA orders and revisions by brand-name manufacturers. Practically, the FDA webpage will facilitate the process. Realistically, many (although not all) generic manufacturers are large companies, including some that also manufacture brand-name drugs and, therefore, have the resources and familiarity with the process to make labeling changes promptly and accurately. For instance, leading generics manufacturer Teva Pharmaceutical Industries "rank(s) among the 10 top pharmaceutical companies in the world" and boasts a 20 percent share of the U.S. generics market, according to the company's website, while brand-name manufacturers Pfizer Inc. and Novartis Corp. have generics divisions that in 2010 ranked as the third and fifth leading generics companies, respectively.[13] In addition, adverse event reports are the most frequent

---

[9] Generic Pharm. Ass'n, *Generic Drug Savings in the U.S.* at 8 (4th ed. 2012).
[10] 78 Fed. Reg. 67985, 67988 (2013) (proposed rule).
[11] *Wyeth v. Levine*, 555 U.S. 555 (2009).
[12] Lester, *supra* note 6, at 303.
[13] *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.

source of labeling changes.[14] These reports are publicly available through the FDA and therefore available to all generic manufacturers.[15]

The concern that the proposed rule would result in confusing or inconsistent labeling is unwarranted. **First**, the FDA has structured the regulation to invite the brand-name manufacturer to submit a revision upon receipt of the generic labeling revision, to allow simultaneous review—with simultaneous approval or other response—of both the generic manufacturer's labeling revision and the corresponding brand-name manufacturer's revision.[16] And the period in which labeling of the brand-name and other generic drugs would differ will be no more than under current regulations (and perhaps less, because the proposed change would specify a 30-day period for conforming changes[17]—whereas today, there is not a specified time for conforming changes). This approach guards against labeling with varied warnings existing beyond a short period, and, in this regard, the process is no different than under current regulations. **Second**, there is no reason to think that, even where several different generic manufacturers are selling the same drug product, the FDA will receive inconsistent labeling revisions. Numerous different newly discovered safety risks are unlikely to come to light for a single drug at the same time. We know this because where there are several distinct drugs within a single class (for example, Prozac, Zoloft, and Paxil, members of a specific class of antidepressants) sold by different brand-name manufacturers, we do not see the manufacturers discovering a variety of new safety risks all at about the same time. If several manufacturers submit changes at or near the same time, the changes are likely to address the same risk. **Third**, for the years 2009-2010, brand-name manufacturers submitted an average of 182 safety-related CBE-0 supplements per year, and approximately 11 per year for drugs also sold in generic form.[18] Although the number would increase under the FDA's proposed rule, the relatively small number of CBE-0 supplements in relation to the approximately 4,000 approved drugs offers an additional reason why concern about a flood of inconsistent CBE-0 submissions is unwarranted. **Fourth**, in the unlikely event that several generic manufacturers submit different CBE-0 supplements at the same time and the FDA sees a risk of confusion, it can promptly review and approve or disapprove each of them, ask manufacturers of that drug not to submit additional updates until the agency has considered those that are pending, or take other appropriate steps to address the matter. The proposal should not be rejected, however, based on hypothetical concerns that current reality suggests may never materialize.

---

[14] Lester, *supra* note 11.
[15] *See* FDA, FDA Adverse Event Reporting System, at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm
[16] *Id.* at 67990.
[17] 78 Fed. Reg. at 67999 (proposed revision to § 314.70(c)(8)(iv)).
[18] FDA Regulatory Impact Analysis, *supra*, at 7, 8.

The argument that the FDA proposal is inconsistent with the Hatch-Waxman Amendments' "sameness" requirement is likewise unfounded. At least since 1985, when the FDA adopted the regulation that allows brand-name manufacturers to revise labeling without prior FDA approval, brand-name and generic labeling have had periods in which they differ, because generic labeling is not updated for months after the brand-name revision. In addition to these temporary differences, long-standing regulations allow for permanent variations—such as the listing of different formulations, different allergy warnings, or omission of a particular use. Thus, the FDA, manufacturers, and patient advocates have long accepted that "sameness" is not to be taken literally, but functionally, as a way to implement Hatch-Waxman's concern that generic and name-brand drugs be equivalent. Adopting an additional exception that applies only temporarily as a means of expediting the provision of updated safety information to physicians and patients is likewise consistent with the Hatch-Waxman Amendments.

Another objection recently made to the FDA's proposal is that, if allowed to make safety-related revisions, manufacturers will over-warn. This objection is also unwarranted. Although brand-name manufacturers have had the ability to make safety updates for more than 30 years, over-warning has not been a problem. As the FDA's Associate Director for Policy, Center for Drug Evaluation and Research (CDER), who has led CDER's Office of Regulatory Policy for more than 20 years,[19] has stated: "We rarely find ourselves in situations where sponsors want to disclose more risk information than we think is necessary. To the contrary, we usually find ourselves dealing with situations where sponsors want to minimize the risk information."[20] Put simply, the FDA "has not experienced problems with sponsors' use of CBE supplements to over warn."[21]

Finally, although allowing generic manufacturers to use the CBE-0 process would also allow the manufacturers to be held accountable to patients for failure to warn, this accountability does not pose the grave problems suggested by generic drug companies. The companies have argued that the proposed rule, when finalized, will expose them to higher insurance premiums to cover liability risk and that some companies may even go out of business or decline to enter the market. Recent history proves this argument wrong.

For all but the last three years, generic drug manufacturers *have* faced liability risk because, until the Supreme Court's *PLIVA v. Mensing* decision in June 2011, generic companies *could* be and *were* sometimes sued for failure to warn of risks posed by their

[19] FDA, About FDA, Jane Axelrad, at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm374540.htm

[20] *FDA Career Staff Objected To Agency Preemption Policies*, United States House Of Representatives, Committee On Oversight And Government Reform, Majority Staff Report 3 (Oct. 2008) (hereafter *FDA Career Staff*).

[21] *Id.*

products. *No court of appeals had accepted the argument that generic drug manufacturers could not be held accountable for failure to warn.* Thus, the proposed rule would not create a *new* cost, but one borne and managed well by the industry consistently until June 2011—and still borne by brand-name manufacturers today.[22]

Further, as the cost per prescription did not drop after the Supreme Court's decision in 2011, there is no basis for assuming that the cost per prescription will rise in light of the new rule. And the recent industry prediction that insurers might refuse to insure generic drug companies against liability risk is flatly contradicted both by the fact that the companies presumably carried such insurance through June 2011 and the fact that brand-name companies continue to face liability risk, and also to obtain insurance, today.

Moreover, the generic manufacturers are wrong to assume that they will incur large liability costs if the proposal is finalized. Rather, with greater ability to make prompt safety updates, the proposed rule should help avoid liability, as compared to the circumstances prior to June 2011 (a period during which the industry grew exponentially), because the rule will help prevent injuries from occurring in the first place.

It is important to keep in mind that lawsuits for failure to warn, when meritorious, occur because a patient suffered injury due to the lack of an adequate warning. For example, the FDA approved the acne medicine Accutane in 1982 and approved the generic form in 2002. The drug has a history of causing significant injury requiring labeling revisions—including warnings about birth defects and mental health risks. Despite reports that the drug can cause inflammatory bowel disease, the brand-name company did not add a warning to the labeling. Finally, in 2009, the FDA ordered that an inflammatory bowel disease warning be added to the label. In the meantime, many patients, often teenagers, developed inflammatory bowel disease, requiring surgeries and altering their lives forever. Because only the brand-name drug could effect labeling changes, none of the many patients who received the generic form can seek compensation from the manufacturers for the thousands of dollars of medical expenses they incurred because of the inadequate warnings. And today, this drug is available in generic-form only is available in generic-form only.[23]

Of course, the manufacturer is not responsible every time that a patient is injured. Sometimes, the patient should not prevail in court. But sometimes, as in the case of Accutane, the manufacturers, including generic manufacturers, had the information but

---

[22] *See* World Health Organization, *Trade, foreign policy, diplomacy and health: Pharmaceutical Industry* (2014), at http://www.who.int/trade/glossary/story073/en/ (10 largest drug companies have profit margins of about 30%); *see also id.* ("Companies currently spend one-third of all sales revenue on marketing their products—roughly twice what they spend on research and development.").

[23] Public Citizen, *supra* note 5, at 11.

turned a blind eye. The current system allows generic manufacturers to do that. The result is more injury and more costs—because immunizing the companies from liability does not make the injured patients' costs go away. The medical expenses and lost wages from lost work time still exist; they are carried by the patients, health insurers, and taxpayers, through Medicare or Medicaid. Because the proposed rule will give generic manufacturers the tools and incentive to update safety labeling, any costs of the rule should be offset by cost savings—savings in medical care for the patients who will not be injured because physicians and patients are armed with updated labeling about safety risks.

Finally, while the objections to the proposed rule center on liability, the primary concern should be with safety. The potential for liability is relevant in this regard because it incentivizes manufacturers to take extra care to ensure that their products are as safe as possible. As FDA's Chief Counsel from 1989 through 2001 stated: "FDA product approval and state tort liability operate independently, each providing a significant, yet distinct, layer of consumer protection. FDA regulation of a [product] cannot anticipate and protect against all safety risks to individual consumers."[24] Similarly, the highest official in FDA's new drug review process in 2008 (a time when the FDA was pro-active in revising regulations for the purpose of immunizing manufacturers from liability) wrote: "[M]uch of the argument for why we are proposing to invoke preemption seems to be based on a false assumption that the FDA approved labeling is fully accurate and up-to-date in a real time basis. We know that such an assumption is false."[25] He continued, "[w]e know that many current approved drug labels are out of date and in many cases contain incorrect information (e.g., the overdose section) ... [I]t is unwise to suggest that FDA approved labeling is always up-to-date and always contains a full and complete listing of all pertinent risk information."[26]

In short, properly used, the revised rule will improve patient safety, and by reducing injuries should also reduce actual instances of litigation as compared to the years before June 2011.

I would be glad to take questions. Thank you.

---

[24] Margaret Jane Porter, *The Lohr Decision: FDA Perspective and Position*, 52 Food & Drug L.J. 7, 11 (1997) (discussing medical device regulation).
[25] *FDA Career Staff, supra* note 20, at 2.
[26] *Id.*

[The supplemental information provided with Ms. Zieve's statement is available at http://docs.house.gov/meetings/if/if14/20140401/101823/hhrg-113-if14-wstate-zievea-20140401.pdf.]

Mr. PITTS. The chair thanks the gentlelady. I will begin questioning. I recognize myself for 5 minutes for that purpose.

Mr. Shumsky, in responding to the bicameral letter sent to the agency in January, FDA decided not to answer the question whether the other sameness requirements included in Sections 505(j) of the Food, Drug, and Cosmetic Act extended beyond the date of approval. Now that FDA has taken the position that the statute does not in fact require sameness in labeling after the date of approval, could it now be argued that the sameness requirements for strength, dosage, route of administration only apply at the time of approval as well? Is this not an absurd result?

Mr. SHUMSKY. Mr. Chairman, thank you for the question. And I think it really hits the nail on the head. It does demonstrate the real absurdity of FDA's proposal because once you take the position that sameness doesn't mean the same for labeling, there is no principle basis for saying that sameness does mean the same for strength, dosage, route of administration, or any of the other requirements in the statute.

Mr. PITTS. Can you please explain why FDA cannot make this change without congressional action?

Mr. SHUMSKY. Sure. There are several reasons, all of which were recognized by the Supreme Court originally in its Mensing decision in 2011 and then its Bartlett decision just this past term, in 2013.

The central statutory provision at issue here is Section 505(j) of the original statute, which specifically says the generic product labeling must be the same as the labeling approved for the brand name drug. There are a couple of other provisions in the statute that are equally relevant. One requires the secretary, which is the secretary of HHS whose vested authority and the Commissioner of food and drugs when it comes to drug approval determinations, it requires the secretary to reject an abbreviated new application, that is a generic drug application, where its labeling is not the same as the branded drug.

And finally, there is a more recent provision of the statute which specifically says that there are certain limited exceptions to the sameness requirement. And we have heard about a couple of them where an inactive ingredient in a product like its coating is different than the brand manufacturer, there are some specific exceptions. None of those exceptions apply to warning or safety-related information and there is a further provision of the statute which says that for certain permissible exceptions, differences between generic and branded labeling will not be considered misbranded if certain criteria are met, but that language in the statute specifically excludes—in other words, it says "but not changes to the warning section of the labeling," which I think represents Congress' explicit recognition that a generic drug which bore different warnings than its branded drug would be misbranded.

Mr. PITTS. Now, some have stated that the proposed rule would simply return the legal landscape for generic drug manufacturers with respect to failure-to-warn cases to where it existed prior to 2011. Therefore, generic manufacturers would assume the same

type of liability they had before the Supreme Court's decision. Is this an accurate assessment?

Mr. SHUMSKY. I don't believe that it is, Mr. Chairman. Prior to 2011, no federal court of appeals had held the generic drug manufacturers could be held liable for failure to warn. To the contrary, one court had addressed that question. In 2008, the Third Circuit Court of Appeals, which is based in Philadelphia, ruled that state failure-to-warn lawsuits targeting generic drug products were preempted. And prior to the Supreme Court's 2009 decision in Wyeth, that was the definitive word in the federal judiciary, in the federal court system on generic liability. Two decisions came after Wyeth, which did expose generic drug manufacturers to liability, one of them was called Mensing out of the Eighth Circuit, the other was called Demahy out of the Fifth Circuit. And as we all know, the Supreme Court promptly reversed both those decisions.

Mr. PITTS. I have one more question I want to ask. Currently, there is a period where the brand and generic drug labeling differs. Usually, this occurs when a brand makes a labeling change on their end and the generic drug manufacturer has to make conforming changes. How is this scenario envisioned under the proposed rule different in nature and scope from what currently takes place?

Mr. SHUMSKY. Sure. It is a totally different situation. Start with the language of the statute, which says the generic drug has to have the same labeling that FDA has approved for the brand. And so there will be a period of time where a brand manufacturer executes one of these CBE–0 changes. FDA then has to consider it and approve it before a generic can implement it. This proposed rule has nothing to do with that scenario. This rule says a generic on its own acting unilaterally can go out, decide it doesn't think that the branded warning is good enough anymore and put a warning onto its product that the brand hasn't considered and that the FDA hasn't reviewed. It is an apples-and-oranges situation.

Mr. PITTS. The chair thanks the gentleman. My time is expired. The chair now recognizes the ranking member, Mr. Pallone, 5 minutes for questions.

Mr. PALLONE. Thank you, Mr. Chairman.

I wanted to ask Ms. Zieve. Today, we have heard a lot about liability and I think it will be important to begin our questions of this panel about the role it plays in this context. So for the benefit of our members, could you describe for us the role that tort liability plays regarding product safety generally, and more specifically, in promoting the safety of drugs and other FDA-regulated products? And could you describe some of the kinds of harm that have been the subject of failure-to-warn lawsuits?

Ms. ZIEVE. Thank you, Mr. Pallone.

I will start by quoting to you from what the Supreme Court has said about state failure-to-warn suits in the drug context. The Court wrote "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 enforce the FDA's premise

that manufacturers, not the FDA, their primary responsibility for their drug labeling at all times."

I think one sort of prominent example of some of the public health benefits beyond for the individual plaintiff comes through the Vioxx cases where a tremendous amount of information came to light only because of the personal injury suits, information that not even FDA had, and it really helped to move that process forward and eventually to get a very dangerous drug off the market and find out what had happened in that case.

There are unfortunately a number of examples of drugs, branded and generic, that have caused serious safety problems. Unfortunately, only, according to one study, about half of serious problems are discovered in the first 7 years after new drug is on the market. So even after the generic comes on the market, we are still finding new safety risks.

I mentioned metoclopramide, which was marketed under the brand name Reglan, in my opening remarks. Another example is Accutane. This one is sort of particularly heartbreaking because the patients who were injured were teenagers. They took the drug for acne. It is purely aesthetic, right, but it is very important to the teenagers. They take this, and unfortunately, it can cause bowel disease that requires in some cases surgery and it can really change their lives permanently and in devastating ways.

And there was information for years and adverse event reports and medical literature that this drug could cause this serious problem and the brand name did nothing. And again, the FDA does not have primary responsibility for labeling updates. It can't. It doesn't have the resources. That is the premise of the Food, Drug, and Cosmetic Act and of the regulations. But the brand name manufacturer said nothing and the generics said nothing because they don't have to.

When the FDA finally ordered a labeling change for Accutane to warn of this serious problem, the brand promptly removed it from the market. So today, this is a drug that has had serious risks added throughout its I think it is 20 or 30 years now on the market and the only products of Accutane sold today are the generic so nobody has responsibility for that labeling today.

Mr. PALLONE. And let me get to my second question. In my opening statement I mentioned that I am sympathetic to the questions surrounding sameness, which is the guiding principle in Hatch-Waxman. How do you respond to the claim that the FDA proposed rule fundamentally violates this sameness principal and will undermine the statutory and regulatory framework for approving and overseeing generic drugs?

Ms. ZIEVE. Well, I am glad you didn't say sameness requirement because, as I mentioned, sameness has never been a requirement. The FDA regulations have a section that lists exceptions to sameness and these have been uncontroversial. The most relevant one is actually during the period after a brand makes a CBE change. The difference between the status quo today and after what I hope will be the FDA finalization of the rule is that that period of difference, that temporary deviation, may be instigated by the generics just like today it is instigated by the brands. And the FDA

has fashioned the rule to make sure that this temporary exception actually works a little more efficiently than it works today.

Mr. PALLONE. All right. I don't know if I have enough time. I think I don't have enough time for my next question now, Mr. Chairman. Thanks.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions.

Mr. LANCE. Thank you, Mr. Chairman.

Ms. Zieve, were you an amicus in either the Mensing or the Bartlett cases or a litigant in some way?

Ms. ZIEVE. My office filed an amicus brief in Mensing——

Mr. LANCE. In Mensing.

Ms. ZIEVE [continuing]. And filed an amicus brief in Bartlett, I believe on behalf of Mr. Waxman.

Mr. LANCE. Thank you. And are you in agreement with the Mensing and the Bartlett decisions?

Ms. ZIEVE. No, I think that they are wrong as a matter of legal jurisprudence as well as policy.

Mr. LANCE. I see. And certainly we can debate policy but you believe the Supreme Court was wrong in both the Mensing and Bartlett decisions?

Ms. ZIEVE. Right, I do, but I also think it is important, particularly in Mensing today that the Supreme Court look to the FDA's regulations and defer to the FDA's view of those regulations in deciding that failure-to-warn suits were preempted. The Court didn't hold that Hatch-Waxman required that result but said specifically it was going to defer to the FDA's view about its own regulations.

Mr. LANCE. Thank you.

Mr. Shumsky, your view on Mensing and Bartlett?

Mr. SHUMSKY. I represented the petitioners in both of those lawsuits and I think the Supreme Court did a fabulous job.

Mr. LANCE. Thank you. Thank you. And this is a situation where the question was litigated to the Supreme Court and the Court made its decision. As I stated to Dr. Hamburg and I think very often in these matters where you stand on issues of public policy is based upon where you sit, if we want to modify the underlying statute, Mr. Shumsky, do you believe we should ask Congress to do that through our statutory power?

Mr. SHUMSKY. I certainly believe that if Congress is of the mind that the public policy here needs to be altered to enable the kind of liability the Mensing and Bartlett decisions——

Mr. LANCE. Yes.

Mr. SHUMSKY [continuing]. Rejected, that Congress needs to act to change the statute to do that. I remain firmly of the belief that FDA has no authority on its own to do that.

Mr. LANCE. Yes.

Mr. SHUMSKY. And I would say I think there are very sound policy reasons underlying the Mensing and Bartlett decisions which would counsel against those changes.

Mr. LANCE. And your testimony would indicate that in the Administration of President Bush, senior President Bush, President Clinton, the junior President Bush, and President Obama, at least at the beginning of his tenure in office, your view was the view

that was prevailing in the administrative agency. Have I got that right?

Mr. SHUMSKY. Yes, Congressman, that is correct.

Mr. LANCE. Thank you. Why in your opinion has there been a change at the agency regarding this matter?

Mr. SHUMSKY. I can't speculate on what has prompted them to turn around after 30 years of taking the position that these labeling changes are impermissible.

Mr. LANCE. And, Mr. Neas, do you have an opinion on that?

Mr. NEAS. It would be speculative. All we have, however, right now is that the FDA after, as Mike said, 30 years of enforcing the law in a certain manner under several different Democratic and Republican administrations made a change, and that change was precisely what the trial lawyers and Public Citizen recommended in 2011 and 2013, and they are the only ones I believe who met with the FDA and think that is a problem.

Mr. LANCE. I am sorry, Ms. Zieve. You are welcome to comment.

Ms. ZIEVE. Sorry. We didn't meet with FDA for what it is worth.

Mr. NEAS. Just the trial lawyers.

Mr. LANCE. The trial lawyers, thank you. They have a perfect right to meet with the FDA.

Mr. NEAS. Absolutely.

Mr. LANCE. Let me be on the record as saying that.

If the rule is finalized, will it likely be a matter of litigation?

Mr. NEAS. If the rule is finalized?

Mr. LANCE. In its current form.

Mr. NEAS. My guess is there is a strong likelihood that it could be the subject of litigation from a variety of different perspectives and constituencies.

Mr. LANCE. And, Ms. Zieve, what is your opinion on that? If the rule is finalized as it has been written, do you believe this is likely to be litigated?

Ms. ZIEVE. Well, I would like to answer that in two ways. I think given what the industry has been saying, it is likely that they are going to want to litigate because they have been saying that they will. But I also think that the rule is perfectly permissible under the Food, Drug, and Cosmetic Act, including the Hatch-Waxman amendments to that act.

Mr. LANCE. Yes, thank you. I realize your opinion but you believe it will be litigated is my question. You think it will be litigated?

Ms. ZIEVE. Well, I believe that the industry has said that they are going to litigate it.

Mr. LANCE. Yes.

And, Mr. Shumsky, do you believe there will be litigation?

Mr. SHUMSKY. It has certainly been discussed but no final decision has been made to the best of my knowledge.

Mr. LANCE. Thank you, Mr. Chairman.

Mr. PITTS. The chair thanks the gentleman and now recognizes the gentleman from Maryland, Mr. Sarbanes, 5 minutes for questions.

Mr. SARBANES. Thank you, Mr. Chairman. I thank the panelists.

I think this is the least absurd proposal to come forward from the FDA I have ever seen. I just wanted to mention that.

I gather there are three basic objections to this rule or critiques of it. One is the increased costs that it represents and I am not convinced that the report that is forecasting those increased costs is based on valid assumptions. But let's assume that there will be increased cost. As an objection to the rule that should be the basis for not going forward, that is a dog that just doesn't hunt because the American public would say it is worth some additional cost in the system to make sure that we are protected. And frankly, the cost that will be saved to whatever industry is involved, as well as in terms of potential damage and harm to individuals and families and patients out there, the cost that will be saved make it worth that investment if you want to look at it in those terms. So I don't think the economic argument is going to carry the day here and I noticed that neither of you lead with that argument, Mr. Shumsky or Mr. Neas, probably because of that reason.

The second objection is the notion that it will create confusion and I read the letter that the pharmacists, among others, submitted to Dr. Hamburg that you cited, Mr. Neas, and they don't outright advocate against this rule. They advise caution and they say the FDA and others need to fully explore the potential unintended consequences that the rule may have on patient access and national healthcare costs, et cetera. And I think that that is exactly what FDA is doing. They are trying to consider what the potential consequences here would be. They are also going to great lengths in the rule to actually reduce the potential for confusion and even reduce it from where it stands now, as I understand it. So I see that as progress.

That then leaves the argument about kind of the statutory interpretation. I don't buy that either because if you subscribe completely to the notion that this sameness principle has to have total integrity, then you would also have to take the position that the brand name manufacturers should not be permitted to put these interim labels on their products as a matter of safety because for some period of time you would be violating a very strict and literal interpretation of the sameness concept because you would have a situation where you would have some drugs that are identical to other drugs that have different labeling on them.

It seems to me it is a very reasonable position for the agency to have taken up until now that sameness ought to be interpreted in context of public safety, and that is why you have had a situation where innovators and brand-name manufacturers have been putting these interim labels on their products even though that for some period of time makes them different from the generic manufacturing labeling because there is an understanding that we are doing the best we can here to protect the public and we have to interpret sameness in the context.

And I think bringing that same perspective and lens, as the agency is now trying to do by making it sensible for the generic manufacturers to also make this change in their labeling for some small period of time, is a perfectly sensible thing to do. And so I guess there are no questions in that. That is just my observation of the matter.

But I continue to support fully the proposal that has been made. I think it is very, very reasonable and I don't think it represents

overreaching of the enforcement or interpretive discretion and authority that the FDA has.

And with that, I yield back.

Mr. PITTS. The chair thanks the gentleman and now recognizes Mr. Braley 5 minutes for questions.

Mr. BRALEY. Thank you, Mr. Chairman.

Mr. Shumsky, in your opening remarks, you made clear that your testimony here today was in your personal capacity. Do you remember that?

Mr. SHUMSKY. Yes, sir.

Mr. BRALEY. Have you or one of your family members ever been harmed by a generic drug?

Mr. SHUMSKY. I have experienced side effects associated with generic drugs. I am not sure I would characterize that or any of my family's experiences as being harmed.

Mr. BRALEY. All right. Have you in your professional capacity ever represented a client who claimed to have been harmed by a generic drug?

Mr. SHUMSKY. No, sir.

Mr. BRALEY. You have represented generic drug manufacturers in front of the Supreme Court, is that correct?

Mr. SHUMSKY. That is correct.

Mr. BRALEY. And were you here in my earlier comments when I talked about a young woman from Ames, Iowa, who had taken a generic drug and had a really bad outcome?

Mr. SHUMSKY. I was, Mr. Congressman.

Mr. BRALEY. OK. This is her picture. Her name is Sophie Howe, and she began having some of the same problems with a complexion medication that we heard mentioned earlier here today, ended up having multiple pulmonary emboli, was hospitalized with that, and had significant complications. At the time she was a college student at Iowa State University, and because of the complications of her injury, she was forced to drop out of school. She had student loans that were paid for and insured by the Federal Government that became due, and that caused her to drop out of a community college program in order to work full-time to pay off her student loans.

So when you walk into the Supreme Court building across the street, you will see a sign up above that says "Equal Justice under Law," but the actual result of the Mensing decision is to tell those claimants like Sophie Howe you have equal justice under the law if you pay more for brand name drugs because she has no remedy under the Court's decision, does she?

Mr. SHUMSKY. Not against the manufacturer of the generic drug product, no.

Mr. BRALEY. Now, Mr. Neas, I want you to know that I am glad that generic drugs are helping American patients by giving them access to affordable medications where and when they need them. And I also believe it is just as important that the medications on the market are safe and that patients and providers are aware of any possible threat to their health. In this Mensing case we have been talking about, were you aware that there was a friend-of-the-court brief filed by 43 state attorneys general talking about the cost-shifting result of not providing this remedy?

Mr. NEAS. I do know that the state attorneys general took a certain decision, sure, as they do.

Mr. BRALEY. In their brief they noted, "Costs should not be shifted to taxpayer-funded healthcare programs. This implied preemption would put added pressure on state and federal budgets. Not only would it be a significant incentive for ensuring the safe use of prescription drugs be eliminated, but injuries to consumers would go uncompensated by the wrongdoer, and much of the resulting increase in healthcare costs would be borne by state-funded programs."

And, Mr. Chairman, I would ask unanimous consent for recognition that the brief was filed by the attorneys general from the States have Minnesota, Louisiana, Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Hawaii, Idaho, Illinois, Indiana, Iowa, Kentucky, Maine, Maryland, Massachusetts, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, Rhode Island, South Carolina, South Dakota, Tennessee, Utah, Vermont, Washington, West Virginia, Wisconsin, Wyoming, and the District of Columbia.

Mr. PITTS. Without objection, so ordered.

Mr. BRALEY. Ms. Zieve, when we are talking about this cost-shifting, are you aware that the same companies that are generic drug manufacturers were held accountable before the Mensing decision either through settlements or through claims in court for failure-to-warn claims?

Ms. ZIEVE. Yes, I am aware that there were hundreds of suits and at least in a few years leading up to Mensing that there were a large number of settlements that are confidential at the manufacturer's request.

Mr. BRALEY. After the Mensing decision, are you aware of any instance where an insurer for one of those generic drug manufacturers rebated portions of premiums that had been paid based on a potential assumption of liability for failure-to-warn claims among generic manufacturers?

Ms. ZIEVE. I am not aware of that. I am also not aware of any decrease in the cost of generics to consumers because of the elimination of liability.

Mr. BRALEY. Thank you, Mr. Chairman. I yield back.

Mr. PITTS. The chair thanks the gentleman. That concludes the questions of the Members.

The ranking member has a unanimous consent request. He will be recognized for that purpose.

Mr. PALLONE. Thank you, Mr. Chairman.

I ask unanimous consent that the Committee include in the record the following: a comment letter to the FDA on the rule by 41 Members of Congress, including myself and Mr. Waxman; New York Times editorial in support of the FDA rule; comment letters to FDA on the rule, well, three, one including the patient and consumer groups and the Consumer Union; the state attorneys general from 30 States, and from an attorney, Brandon Bogle.

Mr. PITTS. Without objection, so ordered.

[The information appears at the conclusion of the hearing.]

Mr. PITTS. That concludes the questions from the Members who are present. We have another hearing going on and I am sure other Members will have questions. We will send those to you in writing. We ask that you please respond promptly.

I remind Members that they have 10 business days to submit questions for the record and I ask the witnesses to respond promptly. Members should submit their questions by the close of business on Tuesday, April 15.

Thank you very much for your testimony today. It has been a very informative hearing.

And without objection, the subcommittee is adjourned.

[Whereupon, at 5:13 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

AARP
Real Possibilities

March 13, 2014

Margaret A. Hamburg, M.D. Commissioner
Food and Drug Administration
Health and Human Services Department
Rockville, MD 20852

Submitted via regulations.gov

Re: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products FDA Docket No. FDA-2013-N-0500 and RIN 0910-AG94

Dear Commissioner Hamburg:

Thank you for the opportunity to comment on the proposed rule on Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products. AARP is a nonprofit, nonpartisan organization, with a membership of nearly 38 million, that helps people turn their goals and dreams into real possibilities, strengthens communities and fights for the issues that matter most to families such as healthcare, employment and income security, retirement planning, affordable utilities and protection from financial abuse.

AARP believes that it is critically important that all prescription drugs carry current and adequate safety warnings. AARP also believes that consumers who are injured by generic drugs should have the same legal rights as consumers who are injured by brand name drugs. We commend the Food and Drug Administration (FDA) for its efforts to enable generic drug manufacturers to make labeling changes so that consumers and prescribers have the most up-to-date and accurate safety information for their prescription drugs.

AARP was extremely concerned by the Supreme Court's ruling that generic drug manufacturers could not be held liable for patient injuries due to inadequate safety information on product labeling because current FDA regulations do not allow generic drug manufacturers to unilaterally update their warning labels (*PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011)*). As noted in AARP's amicus brief in *PLIVA v. Mensing*[1], "Generic drug companies are often in the best position to discover, assess, and take early action to address risks that come to light after the name-brand drug's period of patent exclusivity has ended because, once generic drugs are available, they often have the majority market share for the drug. ... Generic drug manufacturers are already subject to the same requirements as name-brand drugs regarding the "reporting and recordkeeping of adverse drug experiences." 21 C.F.R. § 314.98(a). They should not be immune from liability under

[1] Brief of Public Citizen and AARP as Amici Curiae Supporting Respondents, PLIVA, Inc. v. Mensing, 131 S. Ct. 2567 (2011) (Nos. 09-993, 09-1039, and 09-1501)

state law if they fail to take reasonable steps to ensure that consumers are properly warned about risks from their products."

The current lack of parity in brand name and generic drug manufacturers' ability to update labeling raises serious safety concerns in the current marketplace, where approximately 80 percent of drugs dispensed are generic and, in some instances, the brand name manufacturer exits the market entirely after generic entry. It is essential for generic drug manufacturers to be able to make appropriate updates to their labeling without having to wait for changes to be initiated by a brand name drug manufacturer.

We have reviewed the process FDA laid out in its proposed rule that would allow generic manufacturers to make updates to their labeling when new safety information becomes available. Under the proposed rule, Abbreviated New Drug Application (ANDA) holders would be able to immediately change their labeling when they get new safety information after submitting a "Changes Being Effected" (CBE) supplement to FDA for review and to brand name manufacturer. The new labeling information would be posted to an FDA web page so that it is available to other manufacturers, providers, and consumers. Once the agency approves the change it would also be cleared for the brand name drug, and any other ANDA holders for the same drug product would have to make conforming labeling changes within 30 days.

While AARP wholeheartedly supports the goal of ensuring new drug safety information is available to consumers as quickly as possible, we do have some concerns that the proposed rule could lead to inconsistent labeling information on multiple versions of equivalent drugs for a substantial period of time. The resulting confusion could affect confidence in generic drugs and complicate decision-making conversations between providers and consumers about appropriate drug therapies based on their safety, efficacy and quality.

In addition, while we acknowledge that the new CBE process could speed up the time it takes for generic drug labels to be updated following the approval of a brand name drug's labeling change, it remains unclear how many of these new CBE supplements will be submitted and whether FDA will have the necessary resources to process them expeditiously. Therefore, we believe it will be critical for FDA to closely monitor how generic drug manufacturers and other stakeholders react to the new process and reevaluate how it is working to determine whether any adjustments or improvements are needed.

Thank you for the opportunity to comment on this important proposed rule. If you have any questions, please do not hesitate to contact KJ Hertz on our Government Affairs staff at khertz@aarp.org or 202-434-3770.

Sincerely,

David Certner
Legislative Counsel and Legislative Policy Director
Government Affairs

FDA's Proposed Generic Drug Labeling Rule: An Economic Assessment

By Alex Brill

February 5, 2014

1350 Connecticut Ave. NW | Suite 610 | Washington, DC 20036
www.matrixglobaladvisors.com

EXECUTIVE SUMMARY

On November 13, 2013, the Food and Drug Administration (FDA) released a Proposed Rule that would permit generic drug manufacturers to make changes to their products' labels. Lawmakers and policy experts have raised a number of concerns about the Proposed Rule, including its legality, cost, and impact on patient safety. This study investigates the cost of the Proposed Rule and estimates the impact on public and private generic drug spending should the rule be finalized.

The Proposed Rule would drastically alter the existing legal landscape by eliminating preemption and exposing generic manufacturers, who supply 84 percent of all prescriptions, to product liability lawsuits. This, in turn, would have substantial negative consequences for national health care spending due to the increase in generic drug prices that product liability would induce. Because the FDA fails to consider liability costs for generic manufacturers, the agency reaches the erroneous conclusion that the Proposed Rule would "generate little cost."

In the highly competitive generic pharmaceutical market, additional costs can be expected to result in higher prices. A policy that eliminates preemption and introduces product liability for generic manufacturers would increase manufacturer costs—and generic prices—for the following reasons:

- **Generic manufacturers would face higher insurance premiums**, self-insurance costs, and reserve spending on product liability.
- **Generic manufacturers may exit or decline to enter the market for certain products** for which they perceive greater liability risk or uninsurable liability risks.
- **Insurance companies offering product liability insurance to generic manufacturers may leave the market** when faced with insuring against increased risk, resulting in higher premiums for generic manufacturers.
- **Generic manufacturers would bear the cost of duplicating brand companies' efforts** to monitor for safety-related issues.

Other negative consequences of exposing generic manufacturers to product liability include the incentive it creates for generic manufacturers to "overwarn." The FDA has previously expressed concern about creating this dynamic because the agency is aware that overwarning dilutes the effectiveness of safety labeling and creates confusion for prescribers and patients.

This study offers a conservative estimate of one of the Proposed Rule's negative effects on generic drug manufacturers—and thus patients and payors—by modeling its impact on generic product liability spending. **In brief, the Proposed Rule could be expected to increase spending on generic drugs by $4 billion per year (or 5.4 percent of generic retail prescription drug spending in 2012). Of this, government health programs would pay $1.5 billion, and private health insurance, $2.5 billion.**

Contrary to the FDA's assertion, this study finds that the Proposed Rule would result in an increase in expenditures far in excess of the $141 million threshold for economic significance defined by the Unfunded Mandates Act of 1995. With pharmaceutical spending expected to rise substantially in the coming decade, the economic impact of the Proposed Rule will only increase over time.

INTRODUCTION

On November 13, 2013, the Food and Drug Administration (FDA) released a Proposed Rule titled "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products." If finalized, the rule would permit generic drug manufacturers to make changes to their products' labels, which they currently are prohibited from doing unless the manufacturer of the reference listed drug (RLD) first changes its label. This rule would drastically alter the legal landscape that generic manufacturers face by exposing them to product liability lawsuits. Product liability exposure would in turn have substantial negative consequences for national health care spending. Both public (Medicare, Medicaid, and other programs) and private health insurance spending on generic drugs would increase due to the increase in prices that product liability would induce—a development that the FDA does not take into account in its economic impact assessment.

Lawmakers and policy experts have raised a number of concerns about the Proposed Rule, including its legality, cost, and impact on patient safety. To address the FDA's failure to properly consider cost, this study investigates the economic impact of the Proposed Rule with regard to liability exposure and identifies a multitude of channels—direct and indirect—through which the cost of generic drugs could be affected if the Proposed Rule were finalized. The study then explores in greater detail one such channel and conservatively estimates the increased health care costs that could be expected.

The study is structured as follows. We begin in Section I by contrasting the FDA's stated purpose for the Proposed Rule with the agency's implicit purpose. In Section II, we contrast the FDA's assessment of the Proposed Rule's economic impact with an assessment that incorporates product liability exposure for generic drug manufacturers and the higher prices that would result. In Section III, we provide an overview of total drug spending and generic drug spending and savings in the United States to demonstrate the magnitude of even a small change in generic prices. Having laid this groundwork, we set forth in Section IV the data and methodology we use in our analysis before presenting the results.

In brief, we find that generic product liability would increase spending on generic drugs by $4 billion per year (or 5.4 percent of generic retail prescription drug spending in 2012). Of this, government health programs would pay $1.5 billion, and private health insurance would cover $2.5 billion.

I. PURPOSE OF PROPOSED RULE

According to the FDA, as laid forth in the *Federal Register*, the stated purpose of the Proposed Rule is to "create parity among application holders with respect to these [CBE-0] safety-related labeling changes by permitting ANDA holders to distribute revised generic drug labeling."[1]

However, in the "Preliminary Regulatory Impact Analysis" accompanying the Proposed Rule, the FDA reveals its underlying motivation of addressing a perceived inequity in the ability of consumers to bring suit against drug manufacturers:

> B. Need for Regulation
>
> Two recent Supreme Court cases (*Wyeth v. Levine* and *Pliva v. Mensing*) held that the difference between the NDA [new drug application] and ANDA [abbreviated new drug application] holders'

> abilities to independently change their product labeling leads to different outcomes on whether federal labeling requirements preempt state law tort claims against drug manufacturers for "failure to warn." As a result of these Supreme Court decisions, 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.[2]

The legal authority and regulatory appropriateness of the agency's using rulemaking to create access to the courts are beyond the scope of this study. However, as the next section details, the FDA's own cost-benefit analysis would have differed greatly had the agency considered the economic impact of the true objective of this regulatory change and the associated consequences of the tort claims that would ensue against generic drug manufacturers.

II. Impact of Proposed Rule

We assert that the FDA's assumptions about the Proposed Rule are incomplete and inaccurate, rendering their economic analysis moot. In this section, we identify and discuss the primary failings in the FDA's assumptions before offering our own view of the Proposed Rule's likely economic impact. Beyond the fact that the FDA does not consider the increased liability costs resulting from the Proposed Rule, the agency's logic is riddled with inconsistencies and omissions.

FDA's Assumptions about Proposed Rule's Impact

FDA estimates that the annual net social cost of the Proposed Rule is between $4,237 and $25,852 and further determines that the present discounted value over a 20-year horizon would be between $44,890 and $384,616.[3] This is based on the FDA's estimate that the agency would receive 20 CBE-0 supplements each year from generic manufacturers.[4] More specifically, the FDA estimates a net social cost to ANDA holders between $128 per year and $6,683 per year and a net social cost to NDA holders between $4,109 and $19,169 annually.[5] As a result of the agency's findings, the FDA concludes that the Proposed Rule 1) would not be an economically significant regulatory action, as defined by Executive Order 12866; 2) would not have a significant economic impact on small entities, as defined by the Regulatory Flexibility Act; and 3) would not result in an increase in expenditures of $141 million or more, as set forth by Section 202(a) of the Unfunded Mandates Act of 1995, adjusted by the 2012 Implicit Price Deflator for the Gross Domestic Product.[6]

Among the FDA's flawed and inconsistent assumptions about the Proposed Rule, the following are key to understanding why the agency's economic impact assessment is grossly inadequate and generally incorrect:

1. ***FDA fails to consider liability costs***

As the FDA acknowledges in both the background section of the Proposed Rule and the Preliminary Regulatory Impact Analysis, generic manufacturers are currently protected from product liability suits because they are not allowed to make changes to their product labels. The FDA also acknowledges that the Proposed Rule "may eliminate the preemption of certain failure-to-warn claims with respect to generic drugs."[7] However, the agency fails to consider that eliminating preemption of product liability claims would greatly increase liability risk for generic drug manufacturers, which in turn would lead to substantial price increases for generic drugs. Higher generic drug prices would have a measurable impact on states, the

federal government, private insurance, and consumers. Yet, according to the FDA, "The proposed rule is expected to generate little cost."[8]

The FDA reaches this conclusion because it estimates the annual net social cost of the Proposed Rule based only on the paperwork and administrative burdens on ANDA and NDA holders and assumes "there will be no CBE-0 supplements in addition to the current level submitted by NDA holders each year as a result of the proposed rule."[9] The agency does not estimate any impact from generic product liability and the accompanying price increases on physicians, pharmacists, hospitals, insurers, patients, or public payors such as Medicare or Medicaid. This is a gross oversight on the FDA's part, as the Proposed Rule would, by the agency's own admission, provide patients using generic drugs "access to the courts" to bring failure-to-warn suits against generic manufacturers. And, as explained in greater detail below, such tort liability will impose great cost—direct and indirect—on the generic drug industry, which will result in higher costs, greater risks, and reduced competition among generic drug manufacturers.

In its Preliminary Regulatory Impact Analysis, the FDA acknowledges that there are additional potential costs but excludes them because of "the large amount of uncertainty about how the proposed rule will alter consumer and industry behavior."[10] However, the fact that a cost is uncertain does not justify excluding it or assuming it is zero. To the contrary, uncertainty is itself a burden, and the FDA's inability to quantify certain consequences arising from the Proposed Rule should be considered a cost to stakeholders.

2. FDA believes NDA holders would have more incentive than ANDA holders to initiate label changes

The FDA asserts that "in our base case we expect the NDA holder to desire to be the firm on record for leading a safety-related labeling change."[11] The FDA's reason for this appears to be twofold. First, the agency thinks "the NDA holder [will perceive] its reputation as sufficiently important for it to be in its interest to maintain a reputation for dealing promptly and effectively with safety-related information."[12] Second, the agency assumes that submitting a CBE-0 supplement will be costly enough to discourage ANDA holders from initiating a label change in most instances.

The FDA does note several instances in which an ANDA holder would initiate a label change, including "if, due to a larger market share, the expected economic benefit of moving first is larger [for the ANDA holder] than the expected cost of moving first, or if the expected economic risk of not moving first is larger than the expected cost savings of not moving first."[13] In our opinion, this exception to the FDA's base case should in fact be the base case, as the NDA holder on average has only 5 percent market share of any given multisource product.[14]

The FDA is correct in assuming that every firm can be expected to operate in its own interest. However, the agency fundamentally misrepresents the interests at stake. Drug manufacturers will be driven by their legal obligations and desire to minimize the risk of litigation arising from product liability suits. Potential failure-to-warn suits would provide a strong incentive for every generic manufacturer to be the first to submit a CBE-0 supplement. Therefore, the FDA's assumption that "there will be no CBE-0 supplements in addition to the current level submitted by NDA holders" is implausible, and we should anticipate a far greater impact than the agency's estimate of a shift of 20 CBE-0 supplements from NDA holders to ANDA holders.[15]

In the Preliminary Regulatory Impact Analysis, the FDA mentions in passing that the "likelihood of legal action against the firm for not updating product labeling" could "influence a firm's decision to submit a

CBE-0 supplement," but the agency offers no quantitative analysis.[16] In our opinion, this will be the dominant determining factor in a firm's decision to submit a CBE-0 supplement.

3. FDA asserts that generic insurance premiums will not increase and competition will not decline

At the conclusion of the agency's Preliminary Regulatory Impact Analysis, the FDA simply declares that "generic drug companies purchase insurance to cover a wide range of liabilities, and the cost of covering failure to warn claims will be, as it was in the past, part of an overall insurance cost. Accordingly, we do not anticipate that the proposed rule would result in higher costs to generic drug manufacturers."[17] Because the FDA assumes that generic insurance costs will not increase, the agency also dismisses concerns that the Proposed Rule will induce generic manufacturers to leave or never enter the market.

However, it is illogical for the FDA to acknowledge that ANDA holders are currently exempt from failure-to-warn suits and in the same analysis insist that insurance premiums would not increase if preemption were removed. In addition, the FDA does not acknowledge the variety of ways generic manufacturers approach product liability, including self-insuring and purchasing insurance with very high deductibles. Not only are insurance premiums bound to increase should the Proposed Rule be finalized, but generic manufacturers' direct spending on product liability, through reserve funds and self-insurance, would rise as well.

4. FDA fails to estimate any social benefit from the Proposed Rule

While the mere fact that a Proposed Rule imposes societal costs does not render the rule inappropriate, the premise of cost-benefit analysis for regulatory matters is to demonstrate that the expected benefits of a regulatory action exceed the expected costs. The FDA's analysis fails even to attempt to quantify any expected benefit and instead makes only qualified, qualitative assertions while emphasizing the uncertainty of its predictions.

Specifically, the FDA states, "The public health benefits from adoption of the proposed rule are not quantified. By allowing all application holders to update labeling based on newly acquired information that meets the criteria for a CBE-0 supplement, communication of important drug safety information to prescribing health care providers and the public *could* be improved."[18]

However, Executive Order 13563 expressly directs agencies "to use the best available techniques to quantify anticipated present and future benefits and costs as accurately as possible,"[19] and Executive Order 12866 indicates that an agency should "propose or adopt a regulation only upon a reasoned determination that the benefits of the intended regulation justify its costs."[20] Given that the FDA does not attempt to quantify any public health benefit and does not even express confidence that such a benefit exists, the agency appears not to be acting in accordance with either governing Executive Orders.

Likely Impact of Proposed Rule Considering Generic Drug Liability Exposure

Contrary to the FDA's assertions, we believe that the primary impact of the Proposed Rule would be the elimination of preemption for generic manufacturers and the introduction of the type of product liability that brand drug manufacturers currently face. This policy change would create a drastically altered landscape for generic drug manufacturers—one that would have significant consequences for both private and public U.S. health spending by increasing the prices of generic drugs.

Product Liability and Prices

In any competitive market, producers set their price equal to marginal cost. Therefore, the full burden of an additional cost must be passed forward in the price because the producer price cannot fall below marginal cost. The generic drug industry exhibits many characteristics indicative of a competitive marketplace. Bioequivalence, identical names, lack of advertising or branding, and relatively low cost of entry all indicate a commodity-type marketplace for generic drugs.[21] The FDA's Preliminary Regulatory Impact Analysis affirms the competitiveness of the generic market—the analysis finds that among CBE-0 supplements for NDAs with an ANDA, the average number of approved generic competitors is 8.4.[22]

Given the nature of the generic industry, a policy that eliminates preemption and introduces product liability exposure would increase costs—and therefore generic prices—for the following reasons:

- Generic manufacturers' costs would rise due to higher insurance premiums, self-insurance costs, and reserve spending on product liability.
- Generic manufacturers may exit the market for certain products for which they perceive greater liability risk or uninsurable liability risks. This can be expected to result in generic price increases. As the FDA's own research concludes, "The appearance of a second generic manufacturer reduces the average generic price to nearly half the brand name price. As additional generic manufacturers market the product, the prices continue to fall, but more slowly. For products that attract a large number of generic manufacturers, the average generic price falls to 20% of the branded price and lower."[23]
- Insurance companies offering product liability insurance to generic manufacturers may leave the market when faced with insuring against increased risk, resulting in higher premiums for generic manufacturers, which will in turn be passed on to payors.
- Generic manufacturers would also bear the cost of duplicating brand companies' efforts to monitor for safety-related issues.

Other Effects of Proposed Rule

This study ultimately focuses on the Proposed Rule's price impact, but it is worth noting two other negative consequences of product liability exposure for generic manufacturers. First, generic manufacturers would abstain from entering the market or entirely leave the market for certain products because of liability risk, leaving high-priced brand drugs as the only option. Second, the anticipation of liability claims could induce manufacturers to "overwarn," an inclination that has previously concerned the FDA:

> FDA noted that liability concerns were creating pressure on manufacturers to expand labeling warnings to include speculative risks and, thus, to limit physician appreciation of potentially far more significant contraindications and side effects. . . . Overwarning, just like underwarning, can similarly have a negative effect on patient safety and public health.[24]

In the case of one manufacturer's incentive to overwarn, the primary effect would be to dilute the effectiveness of labeling warnings. However, with multiple manufacturers' responding to this incentive,

the ensuing flurry of label changes for the same product would create confusion among providers and patients, to say the least.

Because the FDA does not incorporate the price effect or any of the other factors identified here in its assessment of the Proposed Rule, the agency does not attempt to quantify their impact. This study is intended to rectify that omission. Our analysis focuses on only one consequence of the Proposed Rule—the impact on generic prices as a direct result of increased liability costs—with the recognition that it is by no means the only negative impact. Indeed, the potential patient safety consequences are a very critical impact of the Proposed Rule, albeit outside the scope of this paper. Before we present our analysis, we offer an overview of current U.S. spending on generic drugs to establish a foundation for understanding the implications of the Proposed Rule's price impact.

III. U.S. Pharmaceutical Spending and Generic Drugs

Generic drugs represent enormous savings for the U.S. health care system. In the last decade, generic drugs have reduced pharmaceutical spending by $1.2 trillion in the United States.[25] In 2012 alone, generics were responsible for $217 billion of savings. Retail prescription drug spending in the United States totaled $263.3 billion in 2012,[26] meaning that without generics, retail prescription drug spending would have been over 82 percent higher.

Generic drugs provide this kind of savings because they constitute a huge share of total prescriptions but at a fraction of the cost of single-source brand products. In 2012, 84 percent of all retail prescriptions were filled with generics, accounting for only 28 percent of total drug spending.[27]

In 2012, government health insurance programs covered 36.8 percent (or $96.9 billion) of all U.S. retail prescription drug spending.[28] Of this, more than 70 percent was borne by Medicare.[29] Because generics account for 28 percent of retail drug spending, government spending on retail prescription generic drugs can be assumed to total $27.1 billion in 2012 alone.

Pharmaceutical spending is expected to increase significantly in the coming decade, as will the government's share of spending. Retail prescription drug spending is projected to rise 73 percent to $455 billion in 2022.[30] During this same period, Medicare spending on retail prescription drugs is projected to rise 115 percent; Medicaid spending, 86 percent; and total government spending, 107 percent. Given this forecast, government health insurance programs will cover 44 percent (or $200.7 billion) of all U.S. retail prescription drug spending in 2022.[31] Assuming that the generic share of pharmaceutical spending remains constant (at 28 percent), total government spending on generics will exceed $56 billion in 2022.

Given the level of government spending on generic drugs, even a small increase in generic prices would have a measurable impact on federal and state spending and thus be detrimental to the long-run viability of Medicare, Medicaid, and other government health care programs. As the preceding section established, liability costs in a competitive marketplace are passed on in the form of higher prices. Therefore, we can be sure that if the Proposed Rule is finalized, we will see an increase in public and private generic drug spending as generic manufacturers pass on new liability costs. In the next section, we estimate the spending increase that the Proposed Rule would induce as a result of this single factor.

IV. Analysis

As we have established, should the FDA Proposed Rule become final, it would expose generic manufacturers to product liability risks and associated legal costs, and these costs would be passed on to consumers and payors in the form of higher prices. In this section, we quantify the impact of increased generic prices on public, private, and out-of-pocket spending as a direct result of increased expected liability costs. To estimate the amount by which generic prices—and thus spending—could be expected to increase due to this new liability exposure, we use the following data and methodology.

In approaching our analysis, we first determine the degree to which the Proposed Rule would expose generic manufacturers to product liability to establish the validity of our hypothesis that it will result in higher costs. Having established this, we then construct a model to estimate the increase in generic spending on product liability.

Generic Product Liability Exposure

To estimate the degree to which generics would face exposure to product liability under the Proposed Rule, we use as a proxy the share of all safety-related label changes that occur after generic entry. The Proposed Rule would expose generic manufacturers to product liability more broadly, but this proxy serves as a conservative measure of exposure.

In the Preliminary Regulatory Impact Analysis, the FDA analyzes CBE-0 supplements from 2009 and 2010 for boxed warnings and contraindications and finds that 39 of the 114 approved changes occurred for products that were available as generics at the time of the label change.[32] In a subsample of CBE-0 supplements including all types of label changes, not just boxed warnings and contraindications, the FDA finds that 27 out of 56 changes occurred for multisource products.[33] Using the following methodology, we conducted an analysis similar to the FDA's but incorporating more recent data and looking at all CBE-0 supplements.

The FDA makes publicly available all safety-related label changes for drugs.[34] We analyzed the most recently available twelve-month period (November 2012 to October 2013). Safety-related label changes are made either with a CBE-0 supplement or a prior approval supplement. Since CBE-0 supplements allow manufacturers to make unilateral changes to their labels and, as such, are the subject of the Proposed Rule, we analyzed only those supplements.

To distinguish between CBE-0 supplements and prior approval supplements, we located the corresponding approval letter, which states what type of supplement the manufacturer submitted, through the FDA's "Drugs@FDA" database.[35] Of the 541 safety-related label changes in the twelve-month period analyzed, 94 were CBE-0 supplements.[36]

To determine which products were available as generics when the label change was made, we cross-referenced the CBE-0 supplements with the Drugs@FDA database, which identifies whether a product has approved therapeutic equivalents. For those drugs with approved therapeutic equivalents, we determined whether a generic version had entered the market using the market date for the first generic manufacturer's participation in Medicaid.[37] An additional step in the analysis was to verify generic market entry with a secondary source, such as a manufacturer press release for the generic launch.

Of the 94 CBE-0 supplements, 40 products were multisource at the time the label change was made. Based on this proxy, we conclude that generic and brand manufacturers would face exposure to product liability to a similar degree.

Modeling Liability-Induced Costs for Generic Manufacturers

Should the proposed FDA rule become final, the product liability and litigation costs to which it would expose generic manufacturers would result in dynamics in the generic drug industry similar to those already observed in the brand drug industry. To estimate the amount that generic manufacturer costs—and thus generic prices—could be expected to increase due to this new liability exposure, we construct a model based on the brand industry.

In a study on medical liability costs for physicians and hospitals, the Government Accountability Office outlines the various types of costs associated with pharmaceutical manufacturer liability and affirms that these costs are reflected in higher prices:

> Manufacturers pass on their liability costs . . . in their products' prices. Their liability costs include insurance and liability-related production and marketing costs. Manufacturer insurance costs . . . can include periodic self-insurance payments, payments made for purchased insurance, and payments made from general revenues to cover uninsured losses. Liability-related production and marketing costs include expenses associated with actions taken primarily to protect the manufacturer from liability, such as multiple layers of packaging and repeated safety warnings.[38]

We conducted an extensive literature review in an effort to determine total product liability spending specific to the brand pharmaceutical industry but found no conclusive estimates. This is in keeping with the Office of Technology Assessment's (OTA) conclusion in 1993 that "the best source of information on the costs and implications of product liability law in this industry are drug companies themselves. The [OTA] found no published data summarizing industry experience."[39] Based on the OTA's direction, we analyzed brand pharmaceutical manufacturer financial statements but did not find consistent reports of product liability spending or product liability insurance premiums.[40]

Given the unfeasibility of quantifying brand drug manufacturers' total spending on product liability, we use average product liability insurance premiums across industries as a proxy. A study published in the *Journal of Political Economy* on the impact of product liability on innovation estimates that product liability insurance premiums for bodily injury represent 0.67 percent of firms' sales.[41]

It should be noted that for the purposes of our analysis, this is a conservative estimate for two reasons: 1) it does not include firms' self-insurance or spending on uninsured losses, and 2) the pharmaceutical industry bears a disproportionate liability burden relative to other industries.[42] Because brand manufacturers typically self-insure,[43] this is not a perfect proxy, but it does approximate product liability spending—and at a level lower than what brand drug companies likely spend on product liability.[44]

To relate drug company sales to drug spending, we use a report from the Bureau of Labor Statistics (BLS) to convert production value to consumption value.[45] According to BLS, U.S. pharmaceutical sales were $300 billion in 2009 (the year reported in the BLS analysis), while U.S. production totaled $177 billion (including

imports and excluding exports). The ratio of production value to consumption value is thus 0.59 ($177 billion/$300 billion). Drug companies' spending on product liability costs (0.67 percent of their revenue) is thus the equivalent of 0.4 percent of consumer spending (0.59 * 0.0067).

Results

In 2012, U.S. retail prescription drug spending totaled $263.3 billion,[46] of which brand drugs represented 72 percent, or $189.6 billion.[47] If the cost of product liability for brand companies equals 0.4 percent of consumer spending, product liability costs in 2012 totaled $758.3 million. Prescriptions in 2012 totaled 4.1 billion, and brand drugs accounted for 16 percent of these, or 652.5 million prescriptions.[48] Therefore, brand product liability spending was roughly $1.16 per prescription in 2012.

Since generics account for 84 percent of all prescriptions (or roughly 3.4 billion prescriptions), generic product liability spending could be expected to total $4 billion (or 5.4 percent of generic retail prescription drug spending in 2012), based on our model. It is worth noting again that our model estimates just one negative economic impact of the Proposed Rule.

Results in Brief

- Total increase in generic drug spending by consumers due to product liability: **$4 billion (5.4 percent)**
  - Increase in government spending: **$1.5 billion (5.4 percent)**
  - Increase in private and out-of-pocket spending: **$2.5 billion (5.4 percent)**

Increase in government spending

As mentioned above, government spending on retail prescription generic drugs was $27.1 billion in 2012. With the introduction of product liability, we could expect government spending to increase $1.5 billion (or 5.4 percent), given that government spending accounts for 36.8 percent of all retail prescription drug spending. The impact on government spending would be higher with the inclusion of Medicare Part B spending (which is excluded here because of the data lag for Part B).

Increase in private and out-of-pocket spending

Private and out-of-pocket spending on generic drugs totaled $46.6 billion in 2012. With the introduction of product liability, we could expect generic spending to increase $2.5 billion, or 5.4 percent, given that private and out-of-pocket spending represents 63.2 percent of all retail prescription drug spending.

As mentioned above, these estimates should be considered conservative given that we use a proxy for product liability insurance premiums that is likely low, do not account for self-insurance and reserve spending, exclude certain drug spending, and do not model the effect of fewer or no generics in a given market. Therefore, while it is difficult to quantify future product liability because of the unpredictability of this type of lawsuit, our results are certainly an underestimate of product liability costs. To depict a far larger but perfectly plausible economic impact on the generic drug industry, we present before concluding a case study of the well-known product liability lawsuits over the brand drug Vioxx.

Case Study: Vioxx

Vioxx was an anti-inflammatory drug that entered the market in mid-1999 and was pulled by Merck & Co., Inc. in September 2004 because of the health risks it posed. During its time on the market, Vioxx recorded more than $11 billion in sales and was used by roughly 20 million Americans.

By 2007, Merck was facing 28,000 Vioxx-related lawsuits and set up a settlement fund of $4.85 billion for qualifying product liability claims. The Vioxx settlement fund was concluded in 2010, with 33,075 plaintiffs receiving compensation.

Had generic versions of Vioxx been available, they could have been expected to comprise 95 percent of the market—and thus 95 percent of the liability. It could thus be assumed that generic manufacturers would have been responsible for $4.6 billion of the $4.85 billion in settlements. Given that generic drugs on average are 80 percent cheaper than brands, settlement costs would have dwarfed sales.

While Vioxx was on the market, it generated annual sales of $2.5 billion, but annual generic sales would have been 20 percent of that, or about $500 million. Over the period that Vioxx was marketed, generic manufacturers' revenue would have been roughly $2 billion, versus Merck's $11 billion.

Since settlement payments depended on the severity of injuries and length of time consumers took Vioxx, a similar settlement agreement would have been necessary for generic manufacturers to settle the same number of claims. Although the revenue generated by brands and generics differs substantially, personal injury claims would have been the same. Thus, generics would have been responsible for $4.6 billion in settlements for a product that generated only $2 billion in revenue.

V. CONCLUSION

In this study, we provide a conservative estimate of just one of many negative economic impacts that the FDA's Proposed Rule would have on generic drug manufacturers and thus patients and payors. According to our analysis, we estimate that imposing liability risk on generic manufacturers would increase generic drug spending by 5.4 percent. For the government, this means an increase in annual generic drug spending of $1.5 billion, and for private payors an increase of $2.5 billion.

Contrary to the FDA's assertion, we find that the Proposed Rule would both be an economically significant regulatory action as defined by Executive Order 12866 and would result in an increase in expenditures far in excess of the $141 million threshold set forth by Section 202(a) of the Unfunded Mandates Act of 1995. Given that pharmaceutical spending is expected to rise, the economic impact of the Proposed Rule will only increase in significance.

About the Author

Alex Brill is the CEO of Matrix Global Advisors, an economic policy consulting firm. He is also a research fellow at the American Enterprise Institute and in 2010 served as an advisor to the Simpson-Bowles Commission. Previously, he was chief economist and policy director to the House Ways and Means Committee. Prior to his time on the Hill, he served on the staff of the President's Council of Economic Advisers.

This report was sponsored by the Generic Pharmaceutical Association. The author is solely responsible for the content. Any views expressed here represent only the views of the author.

NOTES

[1] Food and Drug Administration (FDA), "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," *Federal Register* 78, no. 219 (November 13, 2013), 67985, available at www.gpo.gov/fdsys/pkg/FR-2013-11-13/pdf/2013-26799.pdf.
[2] FDA, "Preliminary Regulatory Impact Analysis: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products" (November 13, 2013), 5, available at www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/UCM375128.pdf. While the Proposed Rule does include similar language, it is buried in the background section (see pp. 67988–9), whereas the Preliminary Regulatory Impact Analysis presents the rationale in its description of the "Need for Regulation."
[3] FDA, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 67986.
[4] *Ibid.*, 67996.
[5] FDA, "Preliminary Regulatory Impact Analysis: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," Table 4.
[6] FDA, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 67995.
[7] *Ibid.*, 67989.
[8] *Ibid.*, 67996.
[9] FDA, "Preliminary Regulatory Impact Analysis: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 16.
[10] *Ibid.*, 18.
[11] *Ibid.*, 11.
[12] *Ibid.*
[13] *Ibid.*, 11–12.
[14] IMS Institute for Healthcare Informatics, "Declining Medicine Use and Costs: For Better or Worse? A Review of the Use of Medicines in the United States in 2012," May 2013.
[15] FDA, "Preliminary Regulatory Impact Analysis: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 13.
[16] *Ibid.*, 12.
[17] *Ibid.*, 19.
[18] FDA, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 67986. (Emphasis added.)
[19] Barack Obama, "Improving Regulation and Regulatory Review," Executive Order 13563 (January 18, 2011), 3821, available at www.regulations.gov/docs/EO_13563.pdf.
[20] Bill Clinton, "Regulatory Planning and Review," Executive Order 12866 (September 30, 1993), available at www.regulations.gov/docs/EO_12866.pdf.
[21] If there are cases within the generic drug industry in which pricing power exists (as may be the case for small generic markets), then prices may rise by more than the increased cost of liability. As economists Don Fullerton and Gilbert Metcalf describe in a paper on the incidence of taxes, "This indirect price effect arises because the decrease in the equilibrium number of firms yields increased market power for the remaining firms." (Don Fullerton and Gilbert Metcalf, "Tax Incidence," in *Handbook of Public Economics, Volume 4*, 1st edition, ed. Alan Auerbach and Martin Feldstein (Amsterdam: Elsevier Science B.V., 2002), 1827.)
[22] FDA, "Preliminary Regulatory Impact Analysis: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," Table 3.
[23] FDA, "Generic Competition and Drug Prices," available at www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/ CDER/ucm129385.htm.
[24] FDA, "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," *Federal Register* 71, no. 15 (January 24, 2006), 3935, available at www.gpo.gov/fdsys/pkg/FR-2006-01-24/pdf/FR-2006-01-24.pdf.
[25] Generic Pharmaceutical Association, "Generic Drug Savings in the U.S.: Fifth Annual Edition," 2013, available at www.gphaonline.org/media/cms/2013_Savings_Study_12.19.2013_FINAL.pdf.

[26] National Health Expenditure Accounts, historical data, Table 2, updated January 7, 2014, available at www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/tables. IMS Health reports that nominal pharmaceutical spending totaled $325.8 billion in 2012. We use National Health Expenditure Accounts data here for consistency in the government's share of spending.
[27] IMS Institute for Healthcare Informatics, "Declining Medicine Use and Costs: For Better or Worse? A Review of the Use of Medicines in the United States in 2012."
[28] National Health Expenditure Accounts, historical data, Table 16. These programs include Medicare, Medicaid, the Children's Health Insurance Program (Titles XIX and XXI), the Department of Defense, and the Department of Veterans Affairs. Other smaller programs such as the Substance Abuse and Mental Health Services Administration and Indian Health Services are not included.
[29] *Ibid.* This does not include drugs reimbursed through Medicare Part B, which totaled $19.5 billion in 2010 (latest data available). See James Cosgrove, "Medicare: Information on Highest-Expenditure Part B Drugs," testimony before the House Subcommittee on Health, June 28, 2013, available at www.gao.gov/assets/660/655608.pdf.
[30] *Ibid.*, "National Health Expenditure Projections 2012–2022," Table 11, available at www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/Proj2012.pdf.
[31] *Ibid.*
[32] FDA, "Preliminary Regulatory Impact Analysis: Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," 13.
[33] *Ibid.*, 7.
[34] FDA, "Drug Safety Labeling Changes," available at www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges.
[35] FDA, "Drugs@FDA: FDA Approved Drug Products," available at www.accessdata.fda.gov/scripts/cder/drugsatfda.
[36] We excluded 24 label changes from the analysis because we were unable to determine whether the source was a CBE-0 supplement or a prior approval supplement, despite consultation with the Division of Drug Information within FDA's Center for Drug Evaluation and Research.
[37] We used the drug product data file for the third quarter of 2013, available at www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Prescription-Drugs/Medicaid-Drug-Rebate-Program-Data.html.
[38] Government Accountability Office (GAO), "Medical Liability: Impact on Hospital and Physician Costs Extends Beyond Insurance" (September 1995), 16, available at www.gao.gov/assets/230/221826.pdf.
[39] U.S. Congress, Office of Technology Assessment, "Product Liability and the Pharmaceutical Industry," in *Pharmaceutical R&D: Costs, Risks and Rewards* (Washington, DC: U.S. Government Printing Office, 1993), 170.
[40] According to GAO, "[Drug and medical device] industry and insurance company officials stated that . . . manufacturers are reluctant to disclose settlement terms for fear of encouraging new suits or inflating future claims. Manufacturers are also reluctant to disclose their pricing strategies because of competition." (GAO, "Medical Liability: Impact on Hospital and Physician Costs Extends Beyond Insurance," 16.)
[41] W. Kip Viscusi and Michael J. Moore, "Product Liability, Research and Development, and Innovation," *Journal of Political Economy* 101, no. 1 (February 1993): 161–84.
[42] W. Kip Viscusi, "Regulatory Reform and Liability for Pharmaceuticals and Medical Devices," in *Advancing Medical Innovation: Health, Safety and the Role of Government in the 21st Century* (Washington, DC: Progress & Freedom Foundation, February 7, 1996), 79–115.
[43] Brief for PhRMA and BIO as Amici Curiae Supporting Petitioner, p. 14, *Wyeth v. Diana Levine*, 555 US 555 (2009).
[44] While the proxy is not perfect, a model based on the brand drug industry is the most appropriate given the unique risks pharmaceutical firms face. According to PhRMA and BIO's brief in *Wyeth v. Levine*, "Insurance experts have observed that 'the pharmaceutical industry presents one of the most volatile risk management challenges in the world of business today'" (p. 14).
[45] Bureau of Labor Statistics, "The Pharmaceutical Industry: An Overview of CPI, PPI, and IPP Methodology," October 2011, available at www.bls.gov/ppi/pharmpricescomparison.pdf.
[46] National Health Expenditure Accounts, "National Health Expenditure Projections 2012–2022," Table 2.
[47] IMS Institute for Healthcare Informatics, "Declining Medicine Use and Costs: For Better or Worse? A Review of the Use of Medicines in the United States in 2012."
[48] *Ibid.*

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

The Honorable Kevin Yoder
House of Representatives
Washington, DC 20515

JAN 2 9 2014

Dear Representative Yoder:

Thank you for your letter of September 20, 2013, cosigned by Representatives Valadao and Nunnelee, requesting information on the Food and Drug Administration's (FDA or the Agency) proposed regulatory changes being considered regarding the labeling of generic drugs. In your letter you expressed concern that the proposed changes might undermine a uniform Federal standard for drug labeling and ultimately affect public safety. We share your concern for public safety.

You specifically requested information related to:

- FDA's notice of proposed rulemaking (NPRM), which would "create parity between" generic and branded drugs (See RIN: 0910-AG94)
- A 2011 citizen petition (Docket Number FDA -2011-P-0675), which was filed with FDA seeking such a change
- FDA's recommendation to the Solicitor General related to the recently filed brief in the United States Supreme Court, (*Mutual Pharmaceutical Co. v. Bartlett*, 133 S.Ct. 2466 (2013)), which stated that "FDA is considering a regulatory change that would allow generic manufacturers, like brand-name manufacturers, to change their labeling in appropriate circumstances."

FDA issued the proposed rule Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products,[1] If finalized, the rule would allow generic drug manufacturers, like brand name manufacturers, to independently update product labeling to reflect certain newly acquired safety information as part of the drug manufacturer's independent responsibility to ensure that its product labeling is accurate and up-to-date. We have attached the proposed rule for your further review.

FDA also issued a response to a citizen petition submitted by Public Citizen on generic drug labeling changes. The petition requested, among other things, that FDA amend its regulations to authorize generic drug manufacturers to revise their product labeling in a manner that differs from the corresponding brand drug through submission of a changes being effected supplement or a prior approval supplement. FDA granted the petition in part and denied the petition in part because the proposed rule, if finalized, would address some (but not all) of the petitioner's requests. The petition also requested that FDA amend the regulations to clarify that all generic

[1] See the *Federal Register*, Vol. 78 p. 67985, November 13, 2013.

drug manufacturers are required to report safety concerns to FDA as soon as they become aware of a clinically significant hazard. FDA denied this request because the current regulations already require such reporting and clearly apply to generic drug manufacturers.

The U.S. Supreme Court decided in *Pliva, Inc. v. Mensing*, 131 S.Ct. 2567 (2011) (*Mensing*) that state law tort claims against a generic drug manufacturer for failure to provide an adequate warning in product labeling were preempted by Federal labeling requirements for generic drugs. The Supreme Court did not adopt the position that the Federal government advocated in *Mensing*. At the request of the Supreme Court, the government filed an amicus brief in that case, addressing the issue of generic preemption. In that brief, the government stated its view that *failure-to-warn* claims against generic drug manufacturers were not categorically preempted because—although generic manufacturers currently may not make unilateral changes to the labeling—generic manufacturers can and must bring safety labeling information to FDA's attention and seek a labeling change when appropriate. However, the Supreme Court held that it was impossible for generic manufacturers to comply with both state and Federal law because they could not independently change their labeling under Federal law to accomplish what the Court found that state law required.

The Supreme Court's decision in *Mensing* prompted FDA to evaluate its current regulations. This decision, as well as the recent decision in *Mutual v. Bartlett*, may alter the incentives for generic drug manufacturers to comply with current statutory and regulatory requirements to conduct robust postmarket surveillance, evaluation, and reporting and to ensure that their product labeling is accurate and up-to-date. In the current marketplace, approximately 80 percent of dispensed drugs are generic drugs, and brand name drug manufacturers may discontinue marketing after generic drug entry. FDA believes it is time to provide generic drug manufacturers with the means to independently update their product labeling to reflect data obtained through postmarket surveillance, even though this will result in temporary labeling differences among products.

All drug and biologics manufacturers—generic as well as brand name—have an ongoing obligation to ensure their product labeling is accurate and up-to-date. The proposed rule would amend FDA's regulations to revise and clarify procedures for application holders to change the labeling of an approved drug or biologic to reflect certain types of newly acquired safety-related information in advance of FDA's review of the change. If this proposed rule is finalized, it would help ensure that health care professionals and the public have access to the most current safety information on the medications they use.

With respect to your request for a description of the resources expended on the proposed rule, this issue, and the proposed rule, involved complex legal and policy issues that required the active engagement of the Center for Drug Evaluation and the Center for Biologics Evaluation and Research as well as the Office of Chief Counsel and offices within the Office of Commissioner. As with other proposed rules, Executive Order 12866 required an analysis of impacts. Processing of the Federal Register document also involved staff time and resources.

With respect to your request for "a detailed listing of any non-government parties the FDA has met with regarding the proposal referenced in the Supreme Court brief and in the NPRM," FDA

generally declined requests for meetings related to this issue pending publication of the proposed rule. Other than through review of the petition described above and of the comments on the petition and of correspondence from members of Congress and the public, FDA did not consult with outside parties. While FDA generally does not participate in a dialogue during the development of proposed rules, there are occasions when FDA staff will participate in a listen-only session with interested parties. FDA's Chief Counsel and others met with Ms. Rooney (American Association for Justice), Mr. Forscey, and Mr. Blizzard on February 15, 2013. This information is publicly available at http://www.fda.gov/NewsEvents/MeetingsConferencesWorkshops/PastMeetingsWithFDAOfficials/ucm340246.htm

The proposed rule issued on November 13, 2013, provides an opportunity for the public to submit comments on FDA's proposal to the public docket established for this rulemaking, and the comment period is being extended until March 13, 2014. We encourage you and other interested parties to review the proposed rule and submit comments to the public docket at www.regulations.gov established for this rulemaking (Docket No. FDA-2013-N-0500).

Thank you, again, for contacting us concerning this important matter. Please let us know if you have further questions. This letter also has been sent to your cosigners.

Sincerely,

Walter S. Harris, MBA, PMP
Deputy Commissioner of Operations and
Chief Operating Officer

Margaret A. Hamburg, MD
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

March 12, 2014

Dear Dr. Hamburg,

Generic medicines are the backbone of America's pharmaceutical market, bringing trillions of dollars in savings for patients and the health care system, and fueling competition and innovation. Patient, physician, pharmacist and payor access to generic medicines rests on the foundation of the Food and Drug Administration's (FDA's) approval of generic medicines as scientifically equal to the brand medicine in drug safety, efficacy and quality. However, the FDA's Proposed Rule on generic labeling could result in multiple versions of labels for the same medicines, which in turn may create uncertainty throughout the drug supply chain.

We fully support a streamlined, efficient process for updating safety information regarding the use of pharmaceutical products for health care practitioners and the general public. However, the Proposed Rule includes revisions to regulations governing generic drugs with respect to both when and how a labeling change would be required that could have unintended negative consequences. For example, the proposed rule creates the regulatory framework whereby multiple, different labeling, including different warnings, can simultaneously exist in the marketplace for multiple generic versions of a drug. This would be inconsistent with FDA's longstanding, unwavering emphasis on consistency in drug labeling and potentially confusing for health care professionals.

As drafted, this Rule also would burden consumers, taxpayers, large and small businesses, and state and federal governments with billions of dollars in increased costs for generic medicines.

A new report by Matrix Global Advisors highlights the significant economic repercussions of this Proposed Rule:

- The Proposed Rule could be expected to increase spending on generic drugs by $4 billion per year (or 5.4 percent of generic retail prescription drug spending in 2012).
- Of this, government health programs could pay an additional $1.5 billion, and private health insurance, $2.5 billion for generic drugs.

The Proposed Rule also may expose pharmacists, physicians, generic drug manufacturers and others in the health care system to substantial new tort liability costs; these, in turn, would require generic manufacturers to adjust prices to stay in business, withdraw products, or decline to launch new affordable versions of brand medicines. This would have a chilling effect on the ability of generic manufacturers and others in the pharmaceutical supply chain to provide affordable medicines to millions of Americans and people across the globe. This is the opposite effect that was intended with the advent of generic medications.

As principals in the health care system, manufacturers must make certain that life-saving medicines include accurate, up-to-date labels for providers, prescribers, caregivers and patients. As a matter of public policy, any proposal to significantly change prescription drug labeling impacts an array of healthcare stakeholders beyond manufacturers – including patients, pharmacists, providers, distributors, group purchasing organizations, and employers.

The FDA and others need to fully explore the potential unintended consequences that the Rule may have on patient access and national health care costs. Permitting labeling changes for generic drugs without FDA approval counters 30 years of law requiring generic and brand medicines to have the same labels.

We believe that simple changes to the proposed rule can achieve all of FDA's objectives related to efficient communication of important safety information. At this critical juncture, we look forward to working with you, and all stakeholders to identify a course of action that does not put patient safety or patient savings at risk.

Sincerely,

Academy of Managed Care Pharmacy (AMCP)
American Association of Colleges of Pharmacy (AACP)
American Pharmacists Association (APhA)
American Society of Health-System Pharmacists (ASHP)
Amerinet
Amerisource Bergen
Cardinal Health
Cardiovascular Research Foundation (CRF)
CVS Caremark
Express Scripts
H. D. Smith
Healthcare Distribution Management Association (HDMA)
Healthcare Supply Chain Association (HSCA)
Innovatix
McKesson Corp.
MedAssets
National Association of Chain Drug Stores (NACDS)
National Coalition on Health Care (NCHC)
Novation
Pharmaceutical Care Management Association (PCMA)
Premier Healthcare Alliance
Rite Aid
Walgreens
Walmart

The labels on generic drugs

Editorial

The FDA should take the lead on making drug-warning labels consistent.

March 12, 2014|By The Times editorial board

When Congress gave generic drugmakers a shortcut onto the market 30 years ago, it required them to provide the same warnings as the brand-name medicines they were copying. Two recent Supreme Court rulings applied that stricture in an unexpected way: Even if generic drugmakers learned of a new side effect, they could not be expected to warn about it unless and until the brand-name drug did. In response, the Food and Drug Administration has proposed a rule to let generic makers add new warnings unilaterally — and allow them to be sued if they don't. One problem with the rule, though, is that it runs counter to the law, which still requires uniform labeling.

When drug manufacturers learn about a bad reaction to one of their products, they have to report it to the FDA — within 15 days if it's serious, less rapidly if it's not — so the agency can decide whether to change the drug's warning label. Brand-name drugmakers have the power to add new warnings temporarily while waiting for the FDA to approve a new label, and to alert physicians about the risk. But the FDA had previously barred generic manufacturers from taking such steps, and the Supreme Court held in 2011 and 2013 that injured patients couldn't sue them for selling unreasonably dangerous products as long as their labels were the same as those on the branded versions.

Fearing that the rulings left generic manufacturers with little incentive to monitor the safety of their products, the FDA has proposed to reverse its stance and allow all drug makers to add temporary warnings without the FDA's approval. The goal is the right one: to make sure doctors and patients are adequately warned about newly discovered risks as soon as possible.

The agency's good intentions, however, don't outweigh the fact that the law doesn't allow generic drugs' labels to vary from the brand-name equivalents'. Allowing each manufacturer of a generic drug to alter its label unilaterally would result in supposedly identical drugs carrying different warnings. That's not only confusing, it would be counterproductive if consumers gravitated away from the generics that carried more daunting — but more up-to-date — warnings.

The FDA is in an awkward position, having relied on manufacturers to take the lead in monitoring drugs after they're approved. But the agency doesn't have the authority to rewrite the 1984 law to give generic manufacturers the same labeling responsibilities that brand-name manufacturers have. Besides, only the FDA has access to all the data that the competing manufacturers compile about drug safety. It should take advantage of its unique vantage point and find a way to update the warning labels for all versions of a drug as needed, simultaneously.

Accessed March 31, 2014

Congress of the United States
Washington, DC 20515

January 22, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
White Oak 32
Silver Spring, MD 20993

Dear Commissioner Hamburg:

We write to express grave concerns regarding a regulation proposed[1] by the Food and Drug Administration (FDA) that would change longstanding policy regarding the 1984 Hatch-Waxman Act (P.L. 98-417). The proposed regulation would allow generic manufacturers to alter an abbreviated new drug application (ANDA) label without the FDA's prior approval. We strongly believe that such a rule would conflict directly with the statute, thwart the law's purposes and objectives, and impose significant costs on the drug industry and healthcare consumers. We respectfully request the Agency explain and reconsider this departure from decades of settled practice.

The Hatch-Waxman Act opened the drug market to competition for the first time and effectively created the modern generic drug industry. Over the course of the past 30 years, the generic drug industry has generated trillions of dollars in healthcare savings. The key to the success of the Hatch-Waxman Act is the requirement for "sameness" with the brand name drug counterpart in all respects—including labeling.[2] By requiring generic drug products to be materially identical to their brand-name counterparts, generic drugs can forego the years of costly tests and clinical trials the branded drug already underwent, and thus offer the same drug at a lower price to patients. For two decades FDA itself has determined that it would violate the statute if generic manufacturers were allowed to deviate from the FDA-approved labeling of the branded drug.[3] Congress has also embraced this settled rule, as we have declined to change it in every food and drug law we have passed since 1992.

---

[1] FDA, *Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products—Proposed Rule*, 78 Fed. Reg. 67985 (Nov. 13, 2008).

[2] The Act requires a generic drug to have the same label, the same active ingredient, the same route of administration, dosage, and strength, and to be bioequivalent to its brand name counterpart. Regarding the generic drug's labeling, the statute requires "the same as the labeling approved for the listed drug referred to in" the sponsor's ANDA. FDCA §§ 505(j)(2)(A)(ii)-(v).

[3] FDA, *Abbreviated New Drug Application Regulations—Final Rule*, 57 Fed. Reg. 17950, 17961 (Apr. 28, 1992); FDA, *Guidance for Industry: Changes to an Approved NDA or* ANDA, at 24 (Apr. 2004). *See also* 21 C.F.R. § 314.150(b)(10) (stating that FDA approval of an ANDA will be withdrawn if the agency finds 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.").

The proposed rule undermines this sameness requirement by allowing generic drug manufacturers to unilaterally revise their safety-related labeling upon submission to the FDA of a "changes being effected" (CBE-0) supplement including the newly acquired information the company believes warranted the changes.[4] After the CBE-0 supplement is submitted, the FDA will evaluate the underlying information submitted, along with other relevant safety data the agency has compiled, and decide whether to officially approve the same labeling changes for the branded product. If approved, all other generics on the market would have 30 days to revise their labeling accordingly. Therefore, multiple FDA-approved, therapeutically equivalent products will at least temporarily be permitted to have different safety-related labeling prior to the FDA determining whether such changes are adequately tailored or warranted at all.

FDA's proposed rule is not only inconsistent with the sameness requirement in the text of the Hatch-Waxman Act, it also threatens to undermine the law's purpose. As the FDA itself has recognized, "Consistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart."[5] Allowing generic manufacturers to unilaterally change their labeling means potentially dozens of drugs that are chemically and biologically identical might nonetheless bear different safety information, confusing patients and prescribers alike. The labeling on the generic products should be identical to the labeling on the branded product so providers and patients are comfortable with the risks and benefits of the product they are using regardless of the name of the company on the bottle or vial.

The Hatch-Waxman law strikes a very important balance between protecting valuable incentives for research and innovation while also encouraging competition in the market. The proposed rule could change that balance and increase the cost of generic and branded drugs. The proposed rule would require generic manufacturers to comply with the new labeling rules without access to the innovator's clinical trial data or the FDA's files, and thus manufacturers cannot possibly know whether the FDA has considered or rejected prior labeling changes. This could result in costly, duplicative testing. Moreover, FDA acknowledges that the proposed rule could increase manufacturer exposure to state tort lawsuits. These costs could be in the billions, and surely will be passed on to the consumer in the form of higher prices. However, the proposed rule estimates the annual cost to be between $4,237 to $25,852. No explanation is given as to how the FDA derived such a low estimate.

To assist the Committee(s) in better understanding the decision making process that led to this proposed rule and to determine whether there are better ways of ensuring patients and providers have timely access to consistent drug safety information, please provide answers to the following questions by no later than February 5, 2014:

1. For the period of time after a generic drug has submitted a CBE-0 supplement, please explain how the generic drug's label will be "the same as the labeling approved for the

[4] Currently, a generic drug manufacturer can only use the CBE-0 supplement process to make changes to its labeling in conformance with the FDA-approved labeling of the branded product.
[5] 57 Fed. Reg. at 17961.

requirements included in sections 505(j)(2)(A)(i)-(v) of the Hatch-Waxman Act extend beyond the date of approval?

2. Please explain the benefit of having proposed label changes published on a public website before FDA consideration, undermining FDA's current role as the gatekeeper and deciding authority for changes to a drug's label.

3. Please provide the names of any executive branch employees outside the FDA who were involved in the decision to proceed with this proposed rule or who participated in drafting or reviewing it.

4. What is FDA's policy on when an adverse event needs to be listed on the label? Are there standards around the prevalence or severity of the adverse event that are necessary before it rises to a labeling change?

5. What is the expected cost to the FDA to review the CBE-0 submissions in a timely manner and establish and update the website, and from where does the FDA propose drawing resources to meet these costs? How will the agency prioritize submissions and what is the estimated time of review?

6. Please describe in detail how FDA arrived at the estimated cost of the rule of $4,237 to $25,852 per year and estimates it will receive 20 CBE-0 supplements annually from approximately 15 ANDA holders. Please explain how the agency derived these estimates. Did FDA conduct any analysis of how long it takes a manufacturer to prepare a CBE supplement and how much it costs? Did FDA conduct any analysis of what it will cost manufacturers to institute new procedures for monitoring safety and effectiveness of drugs? Did FDA conduct any analysis of the effect the proposed rule will have on drug prices? Please provide all documents and communications regarding the cost-benefit analysis.

7. Generic drug manufacturers can currently propose labeling changes with FDA as a result of newly acquired safety information. Please provide statistics for how many times this is done in comparison to brand name manufacturers and the current causes of any delay when using that process. Please provide any evidence that would indicate generic drug manufacturers are not submitting required adverse event reports or otherwise not meeting their post-market surveillance requirements

8. The proposed rule notes a 2010 study of FDA safety-related drug labeling changes that found the median time from initial approval of the drug product to label change was 11 years. Please provide this study and all supporting documentation to the Committee(s). Please also provide statistics showing how long it takes FDA to make a decision once a label change is suggested.

9. Please explain why the prior approval supplement process alone cannot be used effectively to change generic and brand drug labels, and the current causes of any delay when using that process. Please provide any evidence that would indicate generic drug

manufacturers are not updating their label upon FDA approval of a change to the label of the reference brand drug.

10. As an alternative approach, did the FDA consider permitting generic drug manufacturers to use a modified CBE process by which the agency has an opportunity to assess a proposed labeling change before introducing it into the market? What does the agency believe would be the pros and cons of using this approach as opposed to the CBE-0? Did the agency conduct a cost benefit analysis of such an approach?

11. Did the agency consider the impact the proposed rule would have on over-the-counter (OTC) drugs? If so, please submit any such analysis and explain how FDA envisions the proposed regulation applying to OTC drugs.

A number of processes already exist through which generic drug manufacturers can share new safety information and propose a label change to FDA without disrupting the market. If the agency believes those methods are inadequate, it cannot simply ignore written statute. FDA has an obligation to share those concerns with Congress and work together on a legislative solution.

Thank you for your prompt consideration of this important matter. If you have any questions, please have your staff contact Stacy Cline or Grace Stuntz with the Health, Education, Labor, and Pensions Committee at (202) 224-6770 and John Stone, Paul Edattel or Carly McWilliams with the Energy & Commerce Committee at (202) 225-2927.

Sincerely,

Lamar Alexander
Ranking Member
Health, Education, Labor
and Pensions Committee

Fred Upton
Chairman
Energy and Commerce Committee

Michael B. Enzi
United States Senator

Marsha Blackburn
Member of Congress

Richard Burr
United States Senator

John Shimkus
Member of Congress

Johnny Isakson
United States Senator

Joseph R. Pitts
Member of Congress

Orrin G. Hatch
United States Senator

Greg Walden
Member of Congress

Pat Roberts
United States Senator

Tim Murphy
Member of Congress

Lisa Murkowski
United States Senator

Michael C. Burgess
Member of Congress

Mark Kirk
United States Senator

Bob Latta
Member of Congress

Tim Scott
United States Senator

Steve Scalise
Member of Congress

Tom Coburn, M.D.
United States Senator

Phil Gingrey
Member of Congress

Mike Rogers
Member of Congress

Gregg Harper
Member of Congress

Bill Cassidy
Member of Congress

Pete Olson
Member of Congress

David McKinley
Member of Congress

Adam Kinzinger
Member of Congress

Gus Bilirakis
Member of Congress

Bill Johnson
Member of Congress

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

FEB 26 2014

The Honorable Joseph R. Pitts
House of Representatives
Washington, D.C. 20515-3816

Dear Mr. Pitts:

Thank you for your letter of January 22, 2014, cosigned by several of your colleagues, to the Food and Drug Administration (FDA or the Agency), expressing concern with the proposed rule, "Supplemental Applications Proposing Labeling Changes for Approved Drugs and Biological Products," published in the *Federal Register* on November 13, 2013, and available online at *http://federalregister.gov/a/2013-26799*. I should emphasize at the outset that this is a proposed rule and that FDA will be receiving comments on the proposal until March 13 of this year. We will consider those comments carefully and, as with any proposed rule, it is of course possible that FDA might adopt an alternative regulatory approach or that the final rule may differ in some respects from the proposal to reflect points made in the comments. We appreciate your interest in this matter.

We have restated each of your questions below in bold, followed by FDA's responses. Because we have a pending proposed rule concerning these issues, our responses are limited, reflecting statements made publicly in the preamble to the proposed rule.

1. **For the period of time after a generic drug has submitted a CBE-0 supplement, please explain how the generic drug's label will be "the same as the labeling approved for the [brand name] drug" as required by the Hatch Waxman Act? Do the sameness requirements included in sections 505(j)(2)(A)(i)-(v) of the Hatch Waxman Act extend beyond the date of approval?**

At the time of FDA's adoption of the generic drug regulations in 1992, which included the current rules relating to generic drug labeling, FDA believed it was important that product labeling for the reference listed drug (RLD or brand drug) and any generic drugs be the same to assure physicians and patients that generic drugs were, indeed, equivalent to their RLD. However, as the generic drug industry has matured and captured an increasing share of the market, tension has grown between FDA's requirement that a generic drug have the same labeling as its RLD, which facilitates substitution of a generic drug for the prescribed product, and the need for an abbreviated new drug application (ANDA) holder to be able to independently update its labeling as part of its independent responsibility to ensure that the labeling is accurate and up to date.

In the current marketplace, approximately 80 percent of drugs dispensed are generic and, as we have learned, brand 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 post-market surveillance, even though this may result in temporary labeling differences among products while FDA reviews the proposed labeling change. During its review of a generic drug manufacturer's changes being effected (CBE-0) supplement, FDA would consider submissions by the brand drug manufacturer and other generic drug manufacturers related to the safety issue and determine whether the labeling update is justified and whether modifications are needed. FDA would make an approval decision on proposed labeling changes for the generic drug and the corresponding brand drug at the same time, so that brand and generic drug products have the same FDA-approved labeling.

The proposed rule would likely reduce the variation between brand and generic drug labeling that currently takes place. Under current regulations, only brand drug manufacturers can independently update product labeling with certain newly acquired safety information and distribute revised labeling, before FDA reviews or approves the labeling change, by submitting a CBE-0 supplement. Under the current regulation, FDA generally has advised that a generic drug manufacturer may use the CBE-0 supplement process only to update its product labeling to conform to the FDA-approved labeling for the corresponding brand drug or to respond to FDA's specific request to submit a labeling change through the CBE-0 process. Accordingly, while FDA reviews a brand drug manufacturer's CBE-0 supplement, there currently is a difference between the brand drug labeling and generic drug labeling. Once FDA approves a change to the brand drug labeling, the generic drug manufacturer is required to revise its product labeling to conform to the approved labeling of the corresponding brand drug. FDA advises that this update should occur at the very earliest time possible; however, FDA has determined that there is often a delay, of varying lengths, between the date on which revised brand drug labeling is approved and the date on which the generic drug manufacturer submits such labeling updates.

The proposed rule, if finalized, generally would reduce the time in which all generic drug manufacturers make safety-related labeling changes by requiring generic drug manufacturers to submit conforming labeling changes within a 30-day time frame. Please see response to Question 9, for additional information on FDA's examination of the time between approval of an NDA holder's labeling change to include a new boxed warning and submission of the ANDA holder's labeling supplement for conforming changes.

2. Please explain the benefit of having proposed label changes published on a public website before FDA consideration, undermining FDA's current role as the gatekeeper and deciding authority for changes to a drug's label.

If finalized, this rule would help ensure that health care practitioners and the public have access to the most current drug safety information, which may be used to inform treatment decisions based on the balance of potential benefits and risks of the drug product for each patient. The need to promptly communicate certain safety-related labeling changes based on newly acquired information is the basis for the "changes being

effected" exception to the general requirement for FDA approval of revised labeling prior to distribution. Allowing generic drug manufacturers to update product labeling through CBE-0 supplements in the same manner as brand drug manufacturers supports FDA's public health mandate and, as discussed below, does not undermine FDA's authority to decide on whether a labeling change proposed in the CBE-0 supplement should be approved.

The proposed FDA Web page would provide information about pending CBE-0 supplements for safety-related labeling changes, including but not limited to: the active ingredient, the trade name (if any), the application holder, the date on which the supplement was submitted, a description of the proposed labeling change and source of the information supporting the proposed labeling change (e.g., spontaneous adverse event reports, published literature, clinical trial, epidemiologic study), a link to the current labeling for the drug product containing the changes being effected, and the status of the pending CBE-0 supplement (e.g., whether FDA is reviewing the proposed labeling change, has taken an action on the CBE-0 supplement, or has determined that the supplement does not meet the criteria for a CBE-0 supplement).

It is expected that a valid safety concern regarding a generic drug product also would generally warrant submission of a supplement for a change to the labeling by the corresponding brand drug manufacturer, as well as other generic drug manufacturers. The CBE-0 supplements would remain posted on FDA's Web page until FDA has completed its review and issued an action letter. If the CBE-0 supplement is approved, the final approved labeling will be made available on the proposed FDA Web page through a link to FDA's online labeling repository at *http://labels.fda.gov*. After an adequate time period to communicate FDA's decision regarding approval of the CBE-0 labeling supplements and to facilitate submission of conforming CBE-0 supplements by other application holders, as appropriate, the original entry on FDA's Web page would be archived. Approved labeling would continue to be available at *http://labels.fda.gov*.

The proposed FDA Web page is expected to enhance transparency and facilitate public access to new safety-related information for all products—biological products licensed under the Public Health Service Act as well as drug products approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act). The public may subscribe to FDA's free e-mail subscription service to receive an e-mail message each time there is an update to this proposed FDA Web page.

3. Please provide the names of any executive branch employees outside the FDA who were involved in the decision to proceed with this proposed rule or who participated in drafting or reviewing it.

In the course of developing and reviewing FDA proposed regulations, the documents go through a standard clearance review with the Department of Health and Human Services and the Office of Management and Budget, as was the case here.

4. What is FDA's policy on when an adverse event needs to be listed on the label? Are there standards around the prevalence or severity of the adverse event that are necessary before it rises to a labeling change?

The requirements for the content and format of labeling for human prescription drug and biological products are described in FDA's regulations (see 21 CFR 201.56, 201.57, and 201.80; see also the final rule "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products" (71 FR 3922, January 24, 2006) commonly referred to as the "Physician Labeling Rule" (PLR)). FDA's considerations and criteria for inclusion of adverse reactions in the labeling are outlined in two of FDA's guidances for industry: *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format;* and *Adverse Reactions sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format.*

As described in FDA guidance, the WARNINGS AND PRECAUTIONS section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards (e.g., clinically significant drug interference with laboratory tests with subsequent inaccurate test results) that are serious or are otherwise clinically significant because they have implications for prescribing decisions or for patient management. To include an adverse event in this section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established. The BOXED WARNING is ordinarily used to highlight for prescribers those adverse reactions that are so serious in proportion to the potential benefit from the drug that it is essential that they be considered in assessing the risks and benefits of using the drug; *or* those adverse reactions that can be prevented or reduced in frequency or severity by appropriate use of the drug. Boxed warnings are most likely based on observed serious adverse reactions, but there are instances when a boxed warning based on an anticipated adverse reaction would be appropriate.

Adverse reactions that occur with the drug and with drugs in the same pharmacologically active and chemically related class, if applicable, are listed in the ADVERSE REACTIONS section of labeling. FDA's regulations require a separate list for adverse reactions identified from clinical trials and those identified from spontaneous reports after a drug has been marketed. Various factors such as seriousness, severity, frequency, and strength of causal association are used in determining which adverse reactions to include in the ADVERSE REACTIONS section and in characterizing those reactions. Typically, adverse reactions for a given drug will have varying clinical significance (ranging from serious to minor) and certain adverse reactions that have relatively serious clinical implications will be discussed, often in greater detail, in other sections of labeling (e.g., WARNINGS AND PRECAUTIONS).

The PLR and guidances are available at
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm

http://www.fda.gov/downloads/Drugs/Guidances/ucm075096.pdf

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf.

5. What is the expected cost to the FDA to review the CBE-0 submissions in a timely manner and establish and update the website, and from where does the FDA propose drawing resources to meet these costs? How will the agency prioritize submissions and what is the estimated time of review?

In the Preliminary Regulatory Impact Analysis, the Agency made assumptions regarding the number of safety-related labeling changes that will be submitted in CBE-0 supplements. These assumptions were necessary due to the uncertainty about how the proposed rule will alter industry behavior. We assumed that FDA would receive all reports of adverse events required to be submitted and that all drug labeling is eventually updated to reflect important drug safety information, either through a CBE-0 supplement or a prior-approval supplement. We did not estimate the cost to FDA to review a CBE-0 submission, because we view any labeling change initiated by an ANDA holder for a generic drug (rather than a new drug application (NDA) holder for a brand drug) as a transfer across time instead of a change in net cost. Thus, it is a resource-neutral transfer within FDA.

In the Preliminary Regulatory Impact Analysis, we conclude, based on consultations with IT and Communication specialists within FDA, that the creation and maintenance of the Web page devoted to providing information on the CBE-0 supplements for safety-related labeling changes for ANDAs, NDAs, or biologics license applications (BLAs) that are pending FDA action would be routine for FDA staff and would use already established resources. Therefore, we did not include costs to FDA to create or maintain the Web page in the analysis. We acknowledge, however, that if additional resources are needed, the burden to FDA could be between $5,000 and $10,000 to create the page in the first year. We estimate the maintenance burden to be an additional $6,500 to $13,000 per year.

The Agency intends to assess and enhance current procedures for coordinating review of submitted CBE-0 supplements by the relevant review offices to ensure that the proposed labeling changes are acted on in a timely manner, as resources allow. In general, with regard to drug safety issues, FDA prioritizes among these based on factors that include, but are not limited to, the seriousness of the risk; the estimated size of the population exposed to the risk of the drug; the suspected frequency of harm to patients exposed to the drug; the context of the drug's use; the quality of the data suggesting the risk; and the plausibility of a causal relationship between the drug and the risk. FDA anticipates that these and/or similar factors will be considered when prioritizing among the CBE-0 supplement submissions.

6. Please describe in detail how FDA arrived at the estimated cost of the rule of $4,237 to $25,852 per year and estimates it will receive 20 CBE-0 supplements annually from approximately 15 ANDA holders. Please explain

how the agency derived these estimates. Did FDA conduct any analysis of how long it takes a manufacturer to prepare a CBE supplement and how much it costs? Did FDA conduct any analysis of what it will cost manufacturers to institute new procedures for monitoring safety and effectiveness of drugs? Did FDA conduct any analysis of the effect the proposed rule will have on drug prices? Please provide all documents and communications regarding the cost-benefit analysis.

The estimates are fully explained in the Preliminary Regulatory Impact Analysis *http://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm375128.pdf* and in the Paperwork Reduction Act of 1995 section of the proposed rule, *http://www.gpo.gov/fdsys/pkg/FR-2013-11-13/pdf/2013-26799.pdf*, at pp. 67996-97.

7. **Generic drug manufacturers can currently propose labeling changes with FDA as a result of newly acquired safety information. Please provide statistics for how many times this is done in comparison to brand name manufacturers and the current causes of any delay when using that process. Please provide any evidence that would indicate generic drug manufacturers are not submitting required adverse event reports or otherwise not meeting their post-market surveillance requirements.**

FDA cannot readily identify recent examples in which a generic drug manufacturer contacted FDA to propose labeling changes as a result of newly acquired safety information related to the active ingredient. Accordingly, we cannot provide the requested statistics.

We do wish to clarify that the proposed rule focuses on the obligation to update labeling to reflect newly acquired information, not on the legal duties to report adverse drug events to FDA or more generally to meet post-market surveillance requirements associated with adverse event reporting obligations. 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.

Brand and generic drug manufacturers currently have the same requirements for developing written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA. All drug manufacturers (both brand and generic) must promptly review all adverse drug experience information obtained or otherwise received from any source, including published literature, and comply with applicable reporting and recordkeeping requirements. Reporting requirements include submission of 15-day alert reports for serious and unexpected adverse drug experiences, periodic reports, an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling.

8. **The proposed rule notes a 2010 study of FDA safety-related drug labeling changes that found the median time from initial approval of the drug**

product to label change was 11 years. Please provide this study and all supporting documentation to the Committee(s). Please also provide statistics showing how long it takes FDA to make a decision once a label change is suggested.

The 2010 FDA study, "Evaluation of FDA Safety-Related Drug Label Changes," was reported in Pharmacoepidemiology Drug Safety (vol. 22, pp. 302-302, 2013) and is enclosed for your reference.

The Agency relied on the publicly available FDA MedWatch website to obtain a comprehensive list of approved safety-related labeling changes, including drug name, safety issue, and sections of the drug label that were modified between January 1, 2010, and December 31, 2010.

The data to calculate median time to a label change relative to product approval was obtained by retrieving the product approval date and the date of the labeling change for each drug from FDA databases.

The published manuscript of the study contains the basic data and the analyses. Our finding that the median time from approval to a safety-related labeling change in 2010 of 11 years is consistent with that of independent researchers (see Moore TJ, Singh S, Furberg CD. The FDA and New Safety Warnings. Arch Intern Med 2012; 172: 78–80). As we note in the manuscript:

> A recent paper by Moore et al. on 2009 FDA safety warnings found (i) adverse event reports were the most frequent evidence source that supported new regulatory actions and boxed warnings and (ii) the median time from approval to major safety-related regulatory action was 11 years.[] Although Moore et al. reviewed only boxed warnings, warnings, and contraindications for 2009 data and excluded some safety-related regulatory actions and OTC drugs, their findings regarding evidence sources were consistent with our more comprehensive analysis of the data in 2010.

It is important to note that the focus of the FDA study was to characterize the types of drug safety data sources that give rise to post-market safety-related label changes (adverse event reports, clinical trials, observational studies, etc.). It was not to find out the median time from initial approval of a drug product to a label change for all drug products, or a first-time label change for the products reviewed. The 11 years was applicable only to the drug products reviewed in this study.

Because this was a cross-sectional study (i.e., it examined all label changes in calendar year 2010) and not a longitudinal study, the median time to a label change presented in the manuscript is not the median time to the first safety-related labeling change, which may have occurred earlier than the year 2010; this study was just looking at the label changes occurring in 2010. Similarly, it is not a measure of how long it took the company to implement the labeling change. We did not collect information that would allow us to make these measurements.

At this time, we do not have readily available statistics showing how long it takes FDA to make an approval decision on a labeling change proposed in a supplement. In general, FDA aims to review and take action on a supplement submitted by the application holder for a proposed labeling change within 180 days of receipt of the supplement (see regulatory review goals described in 21 CFR 314.100). In certain circumstances, FDA may require certain drug and biological product application holders to make safety-related labeling changes based on new safety information that becomes available after approval (see section 505(o)(4) of the FD&C Act). Section 505(o)(4) of the FD&C Act imposes time frames for application holders to submit and for FDA staff to review such changes, and gives FDA new enforcement tools to bring about timely and appropriate safety labeling changes.

9. Please explain why the prior approval supplement process alone cannot be used effectively to change generic and brand drug labels, and the current causes of any delay when using that process. Please provide any evidence that would indicate generic drug manufacturers are not updating their label upon FDA approval of a change to the label of the reference brand drug.

The need to promptly communicate certain safety-related labeling changes based on newly acquired information is the basis for the "changes being effected" exception to the general requirement for FDA approval of revised labeling prior to distribution. Currently, if a generic drug manufacturer believes that newly acquired safety information should be added to drug product labeling, it must provide supporting information to FDA, and FDA determines whether labeling for both the brand and generic drugs should be revised, which results in a delay in updating generic drug labeling and getting new information to prescribers and patients. FDA's proposed revisions to its regulations, if finalized, would enable generic drug manufacturers to update product labeling promptly to reflect certain types of newly acquired information related to drug safety.

FDA examined new boxed warnings approved during the 2009-2010 time period and found that the time between approval of the NDA holder's labeling change and submission of the ANDA holder's labeling supplement for conforming changes varies, and the majority of ANDA supplement submissions occur after 30 days.[1] Roughly half (30 of 61)[2] of the ANDA supplement submissions for a boxed warning labeling change occurred over 100 days after the NDA's labeling change FDA had approved. ANDA holders currently are advised to submit a CBE-0 supplement to revise product labeling to conform to an approved revision to the reference listed drug's labeling "at the very

[1] Boxed warning labeling changes were the only labeling changes in this review because they represent the strongest labeling changes and we would expect to see the quickest changes to labeling by ANDA holders once the NDA holder's labeling has been changed to reflect the new boxed warning. This is the same time period from which the baseline conditions in the Preliminary Regulatory Impact Analysis are drawn.

[2] Our sample includes 61 approved CBE-0 supplements for changes to the boxed warning of brand drugs for which there was a marketed generic drug at the time of the approved labeling change. Of the 61, there were only seven times where an ANDA holder submitted a labeling supplement to FDA for conforming labeling revisions to the boxed warning within 30 days of the approval of the labeling change supplement submitted by the NDA holder.

earliest time possible" (see guidance for industry on "Revising ANDA Labeling Following Revision of the RLD Labeling" (2000)). The proposed rule would require ANDA holders to submit their revised labeling within 30 days of FDA's posting of the approval letter for the RLD's labeling change on its website.

10. As an alternative approach, did the FDA consider permitting generic drug manufacturers to use a modified CBE process by which the agency has an opportunity to assess a proposed labeling change before introducing it into the market? What does the agency believe would be the pros and cons of using this approach as opposed to the CBE-0? Did the agency conduct a cost benefit analysis of such an approach?

FDA considered several alternatives that would allow certain requirements of the proposed rule to vary, such as proposing a new category of supplements for certain labeling changes being effected in 30 days. However, FDA proposed the regulatory change that it believes would most likely benefit the public health by improving communication of important drug safety information to health care professionals and consumers. Allowing generic drug manufacturers to update product labeling through CBE-0 supplements in the same manner as brand drug manufacturers may improve communication of important, newly acquired drug safety information to prescribing health care professionals and the public. FDA has noted that the U.S. Supreme Court's decision in *Pliva v. Mensing* 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.

11. Did the agency consider the impact the proposed rule would have on over-the-counter (OTC) drugs? If so, please submit any such analysis and explain how FDA envisions the proposed regulation applying to OTC drugs.

The proposed rule applies to over-the-counter (OTC) drug products that are approved in NDAs and ANDAs, but does not apply to OTC drug products marketed under an OTC monograph. The Agency considered the impact that the proposed rule would have on both prescription and OTC drug products approved in NDAs and ANDAs and on biological products licensed in BLAs. FDA's analysis is described in the Preliminary Regulatory Impact Analysis, available at *http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm*

Thank you, again, for contacting us concerning this important matter. Please let us know if you have further questions. The same letter has been sent to your cosigners.

Sincerely,

Sally Howard
Deputy Commissioner
Policy, Planning, and Legislation

Enclosure

Margaret A. Hamburg, MD
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

March 14, 2014

Dear Dr. Hamburg,

The American health care system has a long history of underserving patients of color. While great strides have been made around improving the health of racial and ethnic minority populations through the development of health policies and programs that will help eliminate health disparities, much remains to be done. Generic medicines are a critical part of addressing the access and economic factors which often act as barriers to health care for these populations.

Patient, physician, pharmacist and payor access to generic medicines rests on the foundation of the Food and Drug Administration's (FDA's) approval of generic medicines as scientifically equal to the brand medicine in drug safety, efficacy and quality. Disappointingly, the FDA's Proposed Rule on Generic Labeling, as drafted, would create substantial confusion for pharmacists, doctors, nurses, patients and others in the health care system by allowing for multiple, different drug labels in the market for the very same product, upending 30 years of law and regulation.

This would not only jeopardize patient safety, but as a recent economic study has shown, would also 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 for patients who need them most.

Recent studies have continued to raise serious concerns about the level of generic utilization among lower-income patients about generic drugs. [i] The research suggests that there are cultural barriers to understanding of generic efficacy that can lead patients to miss out on the cost-savings generic medications offer. Even more worrying, this research shows it can lead to dangerous non-compliance. The FDA's Proposed Rule will only add to these challenges.

A new report by Matrix Global Advisors shows that the Proposed Rule would cause spending on generic drugs to increase by $4 billion per year. Of this, government health programs would pay $1.5 billion, and private health insurance, $2.5 billion. These increases would ultimately result in higher patient costs for generic medicines, putting life-saving therapies out of reach for the most vulnerable patients.

The Proposed Rule also may expose pharmacists, physicians, generic drug manufacturers and others in the health care system to substantial new tort liability costs; these, in turn, would require generic manufacturers to adjust prices to stay in business, withdraw products, or decline to launch new affordable versions of brand

medicines. This would have a chilling effect on the ability of generic manufacturers and others in the pharmaceutical supply chain to provide affordable medicines to millions of Americans and people across the globe. This is the opposite effect that was intended with the advent of generic medications.

The FDA and others need to fully explore the potential unintended and harmful consequences that the Rule may have on patient access -- particularly those patient populations currently underserved by our nation's health care system -- and national health care costs. Inclusiveness has to be the operating principle. The FDA should hear from providers who serve racial and ethnic minority populations who could offer expertise, experience, and perspective.

We believe that simple changes to the proposed rule can achieve all of FDA's objectives related to efficient communication of important safety information. At this critical juncture, we look forward to working with you, and all stakeholders to identify a course of action that does not put patient safety or patient savings at risk.

Sincerely,

International Association of Black Professional Fire Fighters

National Alaska Native American Indian Nurses Association (NANAINA)

National Association of Hispanic Nurses

National Black Chamber of Commerce

National Black Nurses Foundation

National Coalition on Black Civic Participation

National Coalition of Ethnic Minority Nurse Associations

National Dental Association

National Minority Quality Forum

Philippine Nurses Association of America

Student National Dental Association

---

[1] *Perceptions of and Barriers to Use of Generic Medications in a Rural African American Population, Alabama,* 2011 Keri Sewell, MPH, Susan Andreae, MPH, Elizabeth Luke, BS, Monika M. Safford, MD *Preventing Chronic Disease,* 2012;9

Margaret A. Hamburg, MD
Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

March 13, 2014

Dear Dr. Hamburg,

Generic medicines provide affordable, life-saving medicines to millions of patients, and save trillions of dollars for consumers and the health care system. Patient, physician, pharmacist and payor access to generic medicines rests on the foundation of the Food and Drug Administration's (FDA's) approval of generic medicines as scientifically equal to the brand medicine in drug safety, efficacy and quality. However, the FDA's Proposed Rule on generic labeling could result in multiple versions of labels for the same medicines, which in turn may create dangerous uncertainty.

As patient advocacy organizations, patient safety is our foremost concern. When it comes to labels for prescription medicines, we have one bedrock principle: **drug labels must be FDA-approved and grounded on scientific evidence.**

The FDA's Proposed Rule on Labeling differs from current law, because for the first time since the passage of the Hatch-Waxman Act, generic drugs could have different labeling from each other and the reference product. Uniform safety information provides certainty for patients, doctors, pharmacists and nurses and assures all healthcare practitioners that they can rely on consistent information to inform their decisions and patient conversations. Identical, FDA-approved labels underscore a critical point — once generic medicines pass through extensive FDA review, they are proven scientifically equal to the brand medicine in terms of safety, efficacy and quality.

By creating a framework under which one drug could have multiple different warning labels, the proposed rule would compromise patient safety. Multiple versions of critical safety information would lead to unnecessary confusion and uncertainty for prescribers and other healthcare professionals, with harmful consequences for patients. Requiring generic manufacturers to make unilateral changes prior to FDA approval will lead to a flood of unnecessary labeling changes. The exaggeration of risk and inclusion of unsubstantiated warnings will cause provider confusion and discourage the use of beneficial treatments.

The Proposed Rule also may create additional financial burdens for pharmacists, physicians, generic drug manufacturers and others in the health care system. These could require generic manufacturers to adjust prices to stay in business, withdraw products, or decline to launch new affordable versions of brand medicines. This would have a chilling effect on the ability of generic manufacturers and others in the pharmaceutical supply

chain to provide affordable medicines to millions of Americans and people across the globe. This is the opposite effect of what was intended with the advent of generic medications.

Patients and healthcare practitioners must continue to have access to consistent, transparent information in order to best inform treatment decisions and promote safety. The FDA's rule as presently drafted could severely undermine those goals and lead to unintended consequences.

We would welcome the opportunity to work with others in the health care system, in a multi-stakeholder collaboration, to assist the FDA in strengthening the current labeling regulations. Inclusiveness has to be the operating principle. The FDA should hear from who could offer expertise, experience, and perspective.

Sincerely,

Attention Deficit Disorder Association (ADDA)

Easter Seals

Institute for Safe Medical Practices

National Alliance of Mental Illnesses (NAMI)

National Association of County Behavioral Health & Developmental Disability Directors (NACBHDD)

Scleroderma Foundation

Veterans Health Council

Vietnam Veterans of America

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225-2927
Minority (202) 225-3641

April 16, 2014

Dr. Janet Woodcock
Director
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Dear Dr. Woodcock:

Thank you for appearing before the Subcommittee on Health on Tuesday, April 1, 2014, to testify at the hearing entitled "Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your answer to that question in plain text.

Also attached are Member requests made during the hearing. The format of your responses to these requests should follow the same format as your responses to the additional questions for the record.

To facilitate the printing of the hearing record, please respond to these questions and requests with a transmittal letter by the close of business on Wednesday, April 30, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachments

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
Committee on Energy and Commerce
House of Representatives
Washington, D.C. 20515-6115

OCT 01 2014

Dear Mr. Chairman:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the April 1, 2014, hearing before the Subcommittee on Health, Committee on Energy and Commerce, entitled "Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling." This letter is a response for the record to questions posed by certain Members of the Committee, which we received on April 16, 2014.

If you have further questions, please let us know.

Sincerely,

Thomas A. Kraus
Associate Commissioner
for Legislation

cc: The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health

We have restated each Member's questions below in bold, followed by our responses.

The Honorable John Shimkus

1. **Electronic distribution of prescribing information for drugs and biologics-known as e labeling-would provide healthcare providers with access to the most up-to date safety and efficacy information for a prescription drug product, which is critical to enhancing patient safety. This policy has enjoyed broad support from this Committee in the past, and has heard from FDA that the agency also supports e-labeling policy.**

   In April 2013, the Subcommittee on Health held a hearing on securing the drug supply chain. At this hearing, Dr. Woodcock testified that e-labeling required a rule making process and noted that FDA planned to issue a proposed rule that year. It is my understanding that the proposed rule was submitted to OMB for review in August 2013, yet it still has not been published. Please share with the Committee the reasons for the delay in publishing this rule. Further, please provide a target date for publication of the proposed rule.

   FDA announced in the fall 2009 Unified Agenda of Regulatory and Deregulatory Action (Unified Agenda) its intention to publish a proposed rule, "Electronic Distribution of Content of Labeling for Human Prescription Drugs and Biological Products" (RIN: 0910-AG18), that would require electronic distribution of professional prescribing information for human drug and biological prescription products in lieu of paper, which is currently used. The information provided in the Unified Agenda presents a forecast of the rulemaking activities that the Agency expects to undertake in the foreseeable future. While we cannot provide you with a specific timeline and generally do not discuss details of a proposed rule's contents prior to the issuance of the proposed rule, this is an issue of importance.

   FDA's impetus for a proposed rule for the electronic distribution of professional prescribing information is the need for more rapid distribution to health care professionals of the most up-to-date information about a prescription drug, including new warnings, contraindications, and directions for use, which would contribute to better care for patients, reduction in medication errors, and improved public health. Currently, the professional prescribing information, containing information for the safe and effective use of the product, is distributed in the form of paper leaflets. Although the information in the professional prescribing information is a valuable resource, it may not contain the most current information because the paper leaflets accompanying a particular drug may have been printed and distributed prior to more recent labeling changes. The printed professional prescribing information that is in the package on pharmacy shelves can be out of date because of any changes that have been made to the labeling subsequent to the distribution of the particular package of drug. Such changes can include new approved uses for a drug already on the market and new safety information detected from post-market use of the drug or from ongoing clinical trials.

   FDA seeks to establish a modern and efficient process to distribute professional prescribing information to health care professionals. Because it takes time to prepare revised paper professional prescribing information, include it in the drug packages, and get those packages into distribution, the

electronic distribution of professional prescribing information would help ensure that health care professionals have immediate access to the most up-to-date information about the safety of marketed drugs. Drug products in distribution are rarely recalled by the manufacturer, solely because changes have been made to the labeling; accordingly "real-time" electronic distribution would foster use of the most up to date labeling information.

OMB review is generally the last significant step in the rulemaking process before publication. We are hopeful that the proposed rule will proceed promptly to publication after OMB's review has been completed. OMB held meetings on this rule on November 7, 2013, January 13, 2014, and February 4, 2014. The public record of those meetings, including submissions provided by the meeting requestors, is available at (*http://www.whitehouse.gov/omb/oira_0910_meetings/*).

2. **Some have questioned whether FDA has the authority to require electronic distribution of prescribing information despite the fact that agency requires electronic submission for multiple filings coming to FDA, including new drug application, abbreviated new drug applications, among others. Do you believe that FDA has clear authority to require electronic labeling of prescribing information? If yes, please explain why.**

FDA generally cannot disclose the contents of a rulemaking document in advance of publication. As with any rulemaking, the proposed rule, when published, will set forth the basis of FDA's authority to implement the proposed changes.

The Honorable Tim Murphy

1. **One of the key principles of the Hatch-Waxman Act is the sameness principle. Under current law, the generic drug product must have the same active ingredient, dosage form, strength, route of administration, and labeling as the brand drug product. In practice this requires all labeling for generic drugs to be the same as labeling for brand products, meaning generic manufacturers are not permitted to make any changes to their labeling that is not consistent with labeling of a brand product. The proposed rule represents a shift in FDA's interpretation of this requirement. Will you please explain why FDA has changed its interpretation of the labeling requirements under Hatch-Waxman?**

At the time of FDA's adoption of the generic drug regulations in 1992, which included the current rules relating to generic drug labeling, FDA believed it was important that product labeling for the reference listed drug (RLD or brand drug) and any generic drugs be the same to assure physicians and patients that generic drugs were, indeed, equivalent to their RLD. However, because the generic drug industry has matured and captured an increasing share of the market, the proposal is based on the conclusion that an abbreviated new drug application (ANDA) holder should be able to independently update its labeling as part of its independent responsibility to ensure that the labeling is accurate and up to date.

In the current marketplace, approximately 80 percent of drugs dispensed are generic and brand drug manufacturers may discontinue marketing after generic drug entry. The proposed rule would

provide ANDA holders with the means to update product labeling to reflect data obtained through post-market surveillance, even though this may result in temporary labeling differences among products while FDA reviews the proposed labeling change. As described in the proposed rule, during its review of a generic drug manufacturer's changes being effected (CBE-0) supplement, FDA would consider submissions by the brand drug manufacturer and other generic drug manufacturers related to the safety issue and determine whether the labeling update is justified and, if so, whether modifications to the labeling in the supplement are needed. FDA would make an approval decision on proposed labeling changes for the generic drug and the corresponding brand drug at the same time, so that brand and generic drug products have the same FDA-approved labeling.

2. **Like brand drug manufacturers, generic drug manufacturers are required under current law to share information with FDA about adverse events resulting from use of their drug product. When this information is reported to FDA, does FDA have the authority currently to require a labeling change for brand and generics if the agency believes an update to the safety information is in the interest of public health? Do you have any reason to believe that generic drug manufacturers are not reporting adverse events to FDA as required by current law? If a generic drug manufacturer does not report adverse events in a timely manner, what penalties are available to FDA to enforce this requirement?**

We do wish to clarify that the proposed rule focuses on the obligation to update labeling to reflect newly acquired information, not on the legal duties to report adverse drug events to FDA or more generally to meet post-market surveillance requirements associated with adverse event reporting obligations. 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.

Brand and generic drug manufacturers currently have the same requirements for developing written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA. All drug manufacturers (both brand and generic) must promptly review all adverse drug experience information obtained or otherwise received from any source, including published literature, and comply with applicable reporting and recordkeeping requirements. Reporting requirements include submission of 15-day alert reports for serious and unexpected adverse drug experiences, periodic reports, an annual report (including a brief summary of significant new information from the previous year that might affect the safety, effectiveness, or labeling of the drug product, and a description of actions the applicant has taken or intends to take as a result of this new information) and, if appropriate, proposed revisions to product labeling.

FDA assesses compliance with the requirements for developing written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA and submission of adverse drug experience reports to FDA through inspections of selected drug manufacturers and contractors working on their behalf. FDA may issue Warning Letters, Untitled Letters, or take other appropriate action based on inspectional observations.

Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) authorizes FDA to require certain drug and biological product application holders to make safety-related labeling

changes based on "new safety information" that becomes available after approval of the drug or biological product. "New safety information" is defined in section 505-1(b) of the FD&C Act. However, it is FDA's view that, notwithstanding the section 505(o)(4) process, the labeling changes process under 21 CFR 314.70 and 601.12 continues to apply to application holders in situations in which the application holder becomes aware of newly acquired information, including in circumstances that meet the criteria for submission of a CBE-0 supplement.

<u>The Honorable Renee Ellmers</u>

1. **The sameness principle is one key tenants of the Hatch-Waxman Act. The generic product must be the same as the innovator product when it comes to active ingredient, dosage form, strength, route of administration, and labeling. Congress put these requirements into place to ensure the public trust in the nation's pharmaceutical supply so that patients who took a generic drug would know that the drug would produce the same clinical effect as the originator product. It appears that the proposed rule guts the fundamental idea of sameness by allowing brands and generics to have different labeling.**

   As a nurse, administering life saving medications to patients can be a matter of proper timing. I am concerned that multiple different versions of labeling, for the same drug, will lead to confusion among practitioners. I am also concerned about the welfare of patients. How would you respond to these concerns?

   The proposed rule would likely reduce the variation between brand and generic drug labeling that currently takes place. Under current regulations, only brand drug manufacturers can independently update product labeling with certain newly acquired safety information and distribute revised labeling, before FDA reviews or approves the labeling change, by submitting a CBE-0 supplement. Under the current regulation, FDA generally has advised that a generic drug manufacturer may use the CBE-0 supplement process only to update its product labeling to conform to the FDA-approved labeling for the corresponding brand drug or to respond to FDA's specific request to submit a labeling change through the CBE-0 process. Accordingly, while FDA reviews a brand drug manufacturer's CBE-0 supplement, there currently is a difference between the brand drug labeling and generic drug labeling. Once FDA approves a change to the brand drug labeling, the generic drug manufacturer is required to revise its product labeling to conform to the approved labeling of the corresponding brand drug. FDA advises that this update should occur at the very earliest time possible, however, FDA has determined that there is often a delay, of varying lengths, between the date on which revised brand drug labeling is approved and the date on which the generic drug manufacturer submits such labeling updates.

   The proposed rule, if finalized, generally would reduce the time in which all generic drug manufacturers make safety-related labeling changes by requiring generic drug manufacturers to submit conforming labeling changes within a 30-day time frame.

2. **Some commentators have recommended that FDA address the Mensing issue by moving to a prior approval system for safety labeling changes for all drugs, both New Drug Applications (NDA's) and Abbreviated New Drug Application (ANDA's), in the**

multisource environment. What do you think of that approach? Did FDA consider it in the course of formulating this proposal?

The need to promptly communicate certain safety-related labeling changes based on newly acquired information is the basis for the "changes being effected" exception to the general requirement for FDA approval of revised labeling prior to distribution. Currently, if a generic drug manufacturer believes that newly acquired safety information should be added to drug product labeling, it must provide supporting information to FDA, and FDA determines whether labeling for both the brand and generic drugs should be revised, which results in a delay in updating generic drug labeling and getting new information to prescribers and patients. FDA's proposed revisions to its regulations, if finalized, would enable generic drug manufacturers to update product labeling promptly to reflect certain types of newly acquired information related to drug safety.

FDA considered several alternatives that would allow certain requirements of the proposed rule to vary. However, FDA proposed the regulatory change that it believed would most likely benefit the public health by improving communication of important drug safety information to health care professionals and consumers. Allowing generic drug manufacturers to update product labeling through CBE-0 supplements in the same manner as brand drug manufacturers may improve communication of important, newly acquired drug safety information to prescribing health care professionals and the public. FDA has received a great deal of public input from various stakeholders during the comment period on the proposed rule. FDA is carefully reviewing the comments that have been submitted to the public docket and will determine next steps based on our analysis of the comments.

3. **Under current law, generic drug manufacturers are required to report serious adverse events regarding their drug products to FDA within 15 days. Is that correct?**

All drug manufacturers (both brand and generic) must promptly review all adverse drug experience information obtained or otherwise received from any source, including published literature, and comply with applicable reporting and recordkeeping requirements. Reporting requirements include submission of 15-day alert reports for serious and unexpected adverse drug experiences.

4. **Has it been brought to your attention that generic drug manufacturers are not meeting their obligations to report adverse events? If yes, what enforcement authority does FDA have currently to ensure that generic drug manufacturers comply with adverse event reporting requirements?**

We do wish to clarify that the proposed rule focuses on the obligation to update labeling to reflect newly acquired information, not on the legal duties to report adverse drug events to FDA or more generally to meet post-market surveillance requirements associated with adverse event reporting obligations. 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.

FDA seeks to ensure compliance with the requirements for developing written procedures for the surveillance, receipt, evaluation, and reporting of post-marketing adverse drug experiences to FDA and submission of adverse drug experience reports to FDA through inspections of selected drug manufacturers and contractors working on their behalf. FDA may issue Warning Letters, Untitled Letters, or take other appropriate action based on inspectional observations. Failure to comply with the adverse event reporting requirements violates Sections 301(e) and 505(k) of the FD&C Act.

5. **As you know, generic manufacturers only have access to scientific and medical evidence for their own products. Generic manufacturers do not have access to clinical trial and post market surveillance data for the brand drug product or another drug manufacturer's product because it is proprietary information. Is it correct that only FDA is in possession of all relevant scientific, clinical information related to the safety and efficacy of any drug product, whether brand or generic? If yes, isn't FDA then best positioned to determine whether an update to the safety information of a brand or generic product is in the interest of public health?**

The need to communicate certain safety-related labeling changes as promptly as possible based on newly acquired information available to manufacturers is the basis for the "changes being effected" exception to the general requirement for FDA approval of revised labeling prior to distribution. Allowing generic drug manufacturers to update product labeling through CBE-0 supplements in the same manner as brand drug manufacturers supports FDA's public health mandate. If finalized, this rule would help ensure that health care practitioners and the public have access to the most current drug safety information, which may be used to inform treatment decisions based on the balance of potential benefits and risks of the drug product for each patient.

As described in the proposed rule, during FDA's review of a generic drug manufacturer's CBE-0 supplement, FDA would consider submissions by the brand drug manufacturer and other generic drug manufacturers related to the safety issue and determine whether the labeling update is justified and whether modifications are needed. FDA would make an approval decision on proposed labeling changes for the generic drug and the corresponding brand drug at the same time, so that brand and generic drug products have the same FDA-approved labeling. FDA has received a great deal of public input from various stakeholders during the comment period on the proposed rule. FDA is carefully reviewing the comments that have been submitted to the public docket and will determine next steps based on our analysis of the comments.

6. **It has come to my attention that back in September, the FDA created a $20 million program to test the safety and quality of generic products. What was the reason for the creation of this program? One of the news articles mentioned that your agency has "acknowledged reports that some people may experience an undesired effect when switching from some brand name drugs to generic versions." FDA's acknowledgement regarding this problem is very troubling to me, particularly from a patient and provider prospective. I am interested in your thoughts on this important patient safety issue.**

A generic drug is the same as a brand-name drug in active ingredient, dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use. FDA requires generic drugs to meet the same high standards for quality, strength, purity, and stability as brand-name drugs.

Regarding your assertion that "FDA created a $20 million program to test safety and quality of generic drugs," you may be referring to FDA's generic drug regulatory science initiative. In July 2012, Congress passed GDUFA (Title III of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112–144)). GDUFA is designed to enhance public access to safe, high-quality generic drugs and reduce costs to industry and patients. To support these goals, FDA agreed in the GDUFA commitment letter to work with industry and interested stakeholders on identifying regulatory science research priorities specific to generic drugs for each fiscal year covered by GDUFA. The commitment letter outlines FDA's performance goals and procedures under the GDUFA program for the years 2012–2017. The commitment letter can be found at *http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282595.pdf*.

The FY 2013 regulatory science research priorities list was developed by FDA and industry and included in the GDUFA commitment letter. To implement the FY 2013 priorities list, the Office of Generic Drugs awarded $17 million in external contracts and grants to initiate new research studies during FY 2013. Four million dollars were allocated to support internal research related to generic drugs. This includes rapid response capabilities through equipment for FDA labs and support for laboratory research fellows at FDA, as well as research fellows to work on data analysis and coordination of internal activities with external grants and contracts.

On June 21, 2013, the Office of Generic Drugs held a public hearing to gain input in developing the FY 2014 regulatory science priorities list. This list was prepared based on internal Center for Drug Evaluation and Research discussions, comments received from this public hearing, and comments submitted to the public docket. The FY 2014 Regulatory Science Priorities are as follows: 1) Postmarket evaluation of generic drugs, 2) Equivalence of complex products, 3) Equivalence of locally acting products, 4) Therapeutic equivalence evaluation and standards, and 5) Computational and analytical tools.

On May 16, 2014, FDA hosted a public hearing to obtain input from industry and other interested stakeholders on the identification of regulatory science priorities for FY 2015. To help fulfill FDA's mission, FDA sought input on the following topics: 1) Current regulatory science challenges that limit the availability of generic drugs, 2) Regulatory science approaches to improve the preapproval evaluation of therapeutic equivalence of generic drugs, 3) Post-approval regulatory science approaches to ensure the therapeutic equivalence of approved generic drugs, 4) Prioritization of FY 2015 regulatory science research topics for generic drugs based on public health impact, and 5) The need for additional or revised draft guidance to clarify FDA's scientific recommendations related to generic drug development. FDA is considering all comments made at this hearing and received through the docket as it develops its FY 2015 GDUFA Regulatory Science Plan. Additional information concerning GDUFA, including the text of the law and the commitment letter, can be found on the FDA web site at *http://www.fda.gov/gdufa*.

Attachment 2 – Member Requests for the Record

During the hearing, Members asked you to provide additional information for the record and you indicated that you would provide that information. For your convenience, descriptions of the requested information are provided below.

The Honorable Joseph R. Pitts

1. **In February of 2013 while FDA was drafting this proposed rule, agency officials met with several plaintiffs lawyers, including at least one representative from the American Association for Justice, also known as the Association of Trial Lawyers of America. In fact, according to FDA's public calendar, one of the agency participants in this meeting was Daniel Siegelman from the Office of the Commissioner, who is himself a former prominent member of trial bar. Would you please provide the Committee with the minutes from this February 2013 meeting?**

   On May 6, 2014, FDA provided responsive documents to the Committee, regarding the Committee's requests on the February 2013 meeting. FDA has identified no record of minutes having been recorded for this meeting.

The Honorable Gus Bilirakis

2. **The FDA frequently issues guidance better informing industry of FDA's expectations. How many guidance documents has FDA issued related to updating of generic drug labeling in the past decade?**

   Guidance documents represent the Agency's current thinking on a particular subject, and are one means by which FDA informs industry of acceptable approaches to comply with applicable statutory and regulatory requirements. Documents related to updating generic drug labeling include the following: Guidance for Industry on Revising ANDA Labeling Following Revision of the RLD Labeling (May 2000), Guidance for Industry on Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements (February 2013), and Guidance for Industry on Safety Labeling Changes – Implementation of Section 505(o)(4) of the FD&C Act (July 2013). FDA also discusses its interpretation of statutory and regulatory requirements and explains its policies regarding compliance with such requirements in preambles to a proposed or final regulation and other Agency statements.

R/D: GHamre and JHarcid, OL 4/17/14
Review and Edit: M. Bernstein and J Weiner, ORP/CDER 4/24/14
Edits incorporated: C Bechtel DEO/CDER 4/28/14
Discuss and Edit: OGD Maryll and J Weiner 4/29/14
Compliance concurred with JWeiner's edits 4/29/14.
Review and clear: MBClarke for OEP/OCD 4/30/14
Edits and Cleared (CBE questions): DBeers, OCC 5/7/14
Edits and Cleared (EDL questions, Shimkus 1 and 2): JFinegan, OCC 5/13/14
Review and Edit (at OL's request): J Weiner, ORP/CDER 8/27/14
Review/clear: D Read, OGD/CDER 9/9/14
Edit: RCunningham, DEO 9/9/14
Edits/Clear: DBeers, OCC, 9/16/14
Incorp. Edits: NAlexander, OL, 9/16/14
Edits/Clear: DSigelman/MVelez, OP, 9/16/14
Incorp Edits: NAlexander, 9/16/14
Edits: CRados, OL, 9/19/14
FT: SGrinder, OL, 9/25/14

G:\WP\CDER Team Letters\CDER 2014\2014-2114 QFRs.doc

G:\WP\CDER ADMIN\Hearings 2014\CBE - Health - 4-1\QFRs\QFRs-EC CBE 040114-FINAL DRAFT.doc

File Copy	Office	Surname	Date	Office	Surname	Date	Office	Surname	Date

FRED UPTON, MICHIGAN
CHAIRMAN

HENRY A. WAXMAN, CALIFORNIA
RANKING MEMBER

ONE HUNDRED THIRTEENTH CONGRESS

Congress of the United States

House of Representatives

COMMITTEE ON ENERGY AND COMMERCE
2125 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–6115
Majority (202) 225-2927
Minority (202) 225-3641

April 16, 2014

Mr. Ralph G. Neas
President and CEO
Generic Pharmaceutical Association
777 Sixth Street, N.W., Suite 510
Washington, D.C. 20001

Dear Mr. Neas:

Thank you for appearing before the Subcommittee on Health on Tuesday, April 1, 2014, to testify at the hearing entitled "Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling."

Pursuant to the Rules of the Committee on Energy and Commerce, the hearing record remains open for ten business days to permit Members to submit additional questions for the record, which are attached. The format of your responses to these questions should be as follows: (1) the name of the Member whose question you are addressing, (2) the complete text of the question you are addressing in bold, and (3) your response to that question in plain text.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, April 30, 2014. Your responses should be mailed to Sydne Harwick, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, D.C. 20515 and e-mailed in Word format to **Sydne.Harwick@mail.house.gov**.

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,

Joseph R. Pitts
Chairman
Subcommittee on Health

cc: The Honorable Frank Pallone, Jr., Ranking Member, Subcommittee on Health

Attachment

GPhA
Generic Pharmaceutical Association

April 30, 2014

The Honorable Joseph R. Pitts
Chairman
Subcommittee on Health
420 Cannon House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health
237 Cannon House Office Building
Washington, DC 20515

Dear Chairman Pitts and Ranking Member Pallone,

GPhA would like to submit the following in response to your recent additional questions for the record for the hearing before the Subcommittee on Health on Tuesday, April 1, 2014, entitled "Examining Concerns Regarding FDA's Proposed Changes to Generic Drug Labeling."

Response to the Honorable Joseph R. Pitts

1. **In the proposed rule, the FDA discusses how recent Supreme Court decisions have altered the incentives for generic manufacturers to comply with post-marketing surveillance and adverse event reporting requirements. It is my understanding that after approval, generic manufacturers still have several obligations under federal law to ensure that their products are safe and properly manufactured, is that correct?**

    a. **All manufacturers must report serious and unexpected adverse events within 15 days and all others quarterly and/or yearly, is that correct?**

    b. **Generic manufacturers must also submit annual reports that address safety and effectiveness issues for their products, is that correct?**

    c. **Is there any evidence that generic manufacturers are not complying with their post-marketing obligations?**

Response

After the FDA approves a generic drug, generic manufacturers still have several obligations under federal law to ensure that their products are safe and properly manufactured. These post-approval safety obligations include adverse event reporting.

Yes, all manufacturers must report serious and unexpected adverse events within 15 days and all others through quarterly and yearly reporting requirements.

Yes, additionally, generic manufacturers must also submit annual reports that address safety and effectiveness issues for their products.

It is my understanding that generic manufacturers are complying with the law, and there is no evidence of which I am aware to suggest that manufacturers are not complying with their post-marketing obligations. FDA has reaffirmed this in written statements. If a company fails to comply with the reporting requirements, the FDA may issue a warning letter. If the problem persists, FDA can bring more severe actions.

Response to the Honorable Henry A. Waxman

Mr. Neas, I regret I was unable to stay for the second panel of our hearing to ask you questions about the economic assessment of the FDA rule performed for GPhA by Alex Brill.

Mr. Brill notes that he was unable to find any conclusive estimates of total product liability spending specific to the brand pharmaceutical industry through a literature review and through an analysis of brand pharmaceutical manufacturer financial statements. He therefore used a 1993 study that estimated that product liability insurance premiums for bodily injury represented 0.67% of an industry's sales. By then converting drug company sales to drug spending, he calculated that total pharmaceutical company spending (brand and generic) on product liability was 0.4% of consumer spending in 2009. He then calculated that brand companies spent $758.3 million in 2012 on product liability coverage. By dividing that cost by 652.5 million prescriptions given for brand drugs, he calculated that brands spent $1.16 per prescription in 2012. By multiplying $1.16 by 3.4 billion prescriptions sold for generic drugs, he calculated that generic companies would spend $4 billion on product liability in 2012. My questions are based on these calculations.

1. **Do all drug manufacturers, brand and generic, carry liability insurance now, even if they are not subject to state tort failure-to-warn liability? For example do they carry insurance to provide coverage if they are sued for patient injury due to misbranding, manufacturing defects of contaminated products.**

   Response

   Yes. In general, generic drug manufacturers currently carry insurance for liability in areas other than state tort failure-to-warn claims. Some generic manufacturers are self-insured. Since GPhA represents generic drug manufacturers, I can only speak to their practices and not others.

2. **What are the estimated costs of the insurance they currently carry?**

   Response

   These costs will vary from company to company due to a variety of factors, including company size and product portfolio.

3. **Are there more recent estimates available of the liability insurance costs across industries than the 1993 model used by Mr. Brill?**

   Response

   I am not aware of more recent estimates of the liability costs across industries. I would note, however, that Mr. Brill indicates that this proxy is conservative. On page 9, he writes, "It should be noted that for the purposes of our analysis, this is a conservative estimate for two reasons: 1) it does not include firms' self-insurance or spending on uninsured losses, and 2) the pharmaceutical industry bears a disproportionate liability burden relative to other industries. Because brand manufacturers typically self-insure, this is not a perfect proxy, but it does approximate product liability spending – and at a level lower than what brand drug companies likely spend on product liability.

4. **Did Mr. Brill survey actual liability costs of generic drug manufacturers in 2012? If so, what were the costs?**

   Response

   I am not aware that Mr. Brill surveyed generic drug manufacturers about actual liability costs in 2012.

5. **If he did not, why not?**

   Response

   Mr. Brill's study was conducted independently. I am therefore not in a position to speak to the methodological decisions he made.

6. **The model calculates that total product liability protection for brand drugs in 2012 was $1.16 per prescription. What percentage of that cost was for protection against failure-to-warn liability? Where in the study is that information provided? What is the basis for that estimate?**

   Response

   It is my understanding that the $1.16 per prescription estimate is a conservative proxy for brand drug product liability costs and should therefore not be understood to encompass total product liability spending. As Mr. Brill says on page 10, "These estimates should be considered conservative given that we use a proxy for product liability insurance premiums that is likely low, do not account for self-insurance and reserve spending, exclude certain drug spending, and do not model the effect of fewer or no generics in a given market."

7. **The study estimates that the liability cost to the generic industry subsequent to finalization of the FDA proposed rule would be $4 billion. What percentage of that**

cost is due specifically to the FDA rule? What is the basis for your estimate? Where in the economic analysis is that information provided?

Response

It is my understanding that the estimate of $4 billion pertains entirely to the FDA proposed rule. As Mr. Brill states in the executive summary, "The Proposed Rule could be expected to increase spending on generic drugs by $4 billion per year."

8. **On what basis did the study conclude that, on a per prescription basis, generic manufacturer liability protection costs after finalization of the FDA rule would be identical to that of brand manufacturers? Are there no additional costs relating to protecting the name of the brand, for example, or because less is known about the safety of a brand when it is first introduced onto the market?**

Response

In the section titled "Generic Product Liability Exposure" beginning on page 8, Mr. Brill analyzes "the degree to which generics would face exposure to product liability under the Proposed Rule" and finds "that generic and brand manufacturers would face exposure to product liability to a similar degree." Furthermore, Mr. Brill cites in this section additional evidence that brand and generic liability would be comparable based on the relative frequency of label changes for multisource products identified in the FDA's Preliminary Regulatory Impact Analysis.

9. **What were the generic manufacturer liability costs prior to the 2011 Pliva v. Mensing Supreme Court decision shielding generic manufacturers from failure-to-warn tort liability? I assume those costs were significant, based on what my staff were hearing from your companies about those costs during the lead-up to the Mensing case. What were their liability costs after the decision?**

Response

As noted previously, liability costs will vary from company to company due to a variety of factors, including company size and product portfolio. These costs would not have changed following the 2011 decision since the Supreme Court merely affirmed the federal preemption of state failure-to-warn claims that already existed.

Response to the Honorable Tim Murphy

1. **According to the proposed rule, this policy change is meant to bring parity between brand drug manufacturers and generic drug manufacturers by allowing generic drug manufacturers to propose labeling changes through the CBE-0 process. Could this proposed rule lead to the same medicines having multiple versions of labels, all with different safety information? Do you believe that having different labels for the same drug product could cause confusion for patients and providers?**

Response

Yes, having multiple labels would cause confusion for patients and providers. Although the proposed rule purports to create parity between brand name and generic drug manufacturers with respect to updating labeling, the actual effect will be massive confusion for providers and patients. Generic manufacturers only have access to the scientific and medical evidence for their individual products. They do not have access to the clinical trial data and other proprietary information of the brand manufacturer or current information and data from other generic manufacturers. Only the FDA has access to all the data and information. A generic manufacturer that unilaterally changes its label therefore does so with incomplete information. The proposed rule, however, would allow all generic manufacturers to propose labeling changes. On average, there are eight generic versions for each branded product. If each generic proposes a different labeling change, there could very well be eight different labels for the same molecule. If these labeling change submissions are staggered and not all together, it may be impossible for the molecule to have consistent labeling. Multiple versions of critical safety information would lead to unnecessary confusion and uncertainty for prescribers and other healthcare professionals, with harmful consequences for patients.

More than twenty companies and organizations within the pharmaceutical supply chain – pharmacists, wholesalers, PBM's, chain drug stores – as well as patient advocacy, disability, veterans, and minority organizations have expressed concern that the proposed rule could result in multiple versions of labels for the same medicine, which in turn may create uncertainty throughout the drug supply chain.

The generic industry and others have worked hard at ensuring consumer confidence in generic drugs and that the generic and brand will produce the same clinical effect. Prescribers and consumers have tremendous confidence in generic drugs because the FDA approves them as the same – bioequivalent – to the referenced brand drug. Allowing different warning labels between the brand and the generic threatens to undermine consumer confidence in generic medicines, potentially decreasing their use and eroding savings to the health care system. Up until last year, the FDA has consistently stated that uniform labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its branded counterpart.

2. **Ensuring that the same medicines have uniform safety information ensures that all health care providers and patients have the same information about the medicine whether it be brand or generic. Do you believe that under the proposed rule, generic drug manufacturers will lead to more, not less, labeling changes whenever new safety information about a drug product comes to light? Please explain.**

Response

The proposed rule creates an incentive for both brand and generic manufacturers to put more warnings on the labeling in order to protect themselves against failure to warn claims. Many of our smaller generic companies, which only have a handful of products,

cannot absorb the cost of a failure-to-warn suit. In an effort to protect themselves from such potential litigation, companies may overwarn on the labeling. As you know, the FDA for years has opposed adding warnings for the sake of adding warnings because it could downplay the importance of the warning, or physicians could stop reading the labeling all together.

GPhA and its members are committed to ensuring the public's health. Sound medical and scientific evidence should guide any type of labeling change.

Response to the Honorable Renee Ellmers

1. **According to the FDA, the estimated proposed annual cost if this rule were to be implemented, to generic manufactures is between $128 and $6,683 per year. However, a recent study sponsored by GPhA found that the proposed rule would increase U.S. health care costs by $4 billion annually. Will you explain some of the reasons why this study estimates much higher costs than FDA?**

Response

The proposed rule would burden consumers, taxpayers, businesses, and state and federal governments with billions of dollars in increased costs for generic medicines by inundating the marketplace with multiple versions of labels for the same medicines. An analysis by economic consulting firm Matrix Global Advisors found that the proposed prescription drug labeling rule would add $4 billion dollars annually to the nation's already high health care costs. Of the projected increase in health care costs, the analysis estimates that Medicare and other government programs will incur $1.5 billion in annual new spending, while private insurers and patients will pay $2.5 billion per year.

The proposed rule would expose generic drug manufacturers to substantial new tort liability costs, which in turn would require them to adjust prices to stay in business, withdraw products, or decline to launch new affordable versions of brand medicines. Increased liability would also accrue to pharmacists, physicians and other participants in the health care system, beyond the substantial confusion for all stakeholders, impeding health care decisions and delivery.

The result would be fewer generic drugs coming to market and manufacturers withdrawing from certain high-risk markets, leading to drug shortages, the underutilization of affordable generics medicines, and ultimately increased prescription drug spending.

Unfortunately, neither the FDA nor the Office of Management and Budget (OMB) conducted an appropriate cost-benefit analysis – as OMB is required to do – to examine any of these potential pitfalls and increased costs. The FDA overlooked the proposed rule's very real financial impact on the affordability and availability of generic medications for patients and all stakeholders in the drug supply chain.

2. **In the proposed rule, FDA suggests that only 20 or so labeling changes would be submitted by generic manufacturers annually if the rule went into effect. Do you believe that this is an accurate assessment of how many labeling changes would be submitted annually under this proposed change? Would you agree that the proposed rule could lead to more, not less, labeling changes by generic drug manufacturers as new safety information comes to their attention?**

   Response

   I do not believe the FDA assessment of only 20 labeling changes per year is accurate. As you know, this proposed rule would allow generic drug manufacturers to propose labeling changes. On average, there are eight generic versions for each branded product. If each generic proposes a different labeling change, there could very well be eight different labels for the same molecule. If these labeling changes come in staggered and not all together, it may be impossible for the molecule to have consistent labeling. This would result in patient and provider confusion.

Thank you again for the opportunity to testify before the Subcommittee.

Sincerely,

Ralph G. Neas
President and CEO