

EXAMINING MEDICAL PRODUCT MANUFACTURER COMMUNICATIONS

HEARING BEFORE THE SUBCOMMITTEE ON HEALTH OF THE COMMITTEE ON ENERGY AND COMMERCE HOUSE OF REPRESENTATIVES ONE HUNDRED FIFTEENTH CONGRESS FIRST SESSION

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¹ Dr. Kesselheim and Ms. Khachatourian did not answer submitted questions for the record by the time of printing.

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EXAMINING MEDICAL PRODUCT MANUFACTURER COMMUNICATIONS

WEDNESDAY, JULY 12, 2017

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

The subcommittee met, pursuant to call, at 10:18 a.m., in Room 2322, Rayburn House Office Building, Hon. Michael C. Burgess (chairman of the subcommittee) presiding.

Members present: Representatives Burgess, Guthrie, Barton, Upton, Shimkus, Blackburn, Lance, Griffith, Bilirakis, Bucshon, Brooks, Mullin, Hudson, Collins, Carter, Walden (ex officio), Green, Engel, Schakowsky, Butterfield, Matsui, Castor, Sarbanes, Kennedy, Cárdenas, Eshoo, and Pallone (ex officio).

Staff present: Adam Buckalew, Professional Staff Member, Health; Daryll Dykes, Health Fellow; Paul Edattel, Chief Counsel, Health; Adam Fromm, Director of Outreach and Coalitions; Jay Gulshen, Legislative Clerk, Health; Alex Miller, Video Production Aide and Press Assistant; Jennifer Sherman, Press Secretary; Danielle Steele, Policy Coordinator, Health; John Stone, Senior Counsel, Health; Hamlin Wade, Special Advisor for External Affairs; Jeff Carroll, Minority Staff Director; Samantha Satchell, Minority Policy Analyst; Andrew Souvall, Minority Director of Communications, Member Services, and Outreach; Kimberlee Trzeciak, Minority Senior Health Policy Advisor; and C.J. Young, Minority Press Secretary.

Mr. BURGESS. The Subcommittee on Health will now come to order. I will recognize myself for 5 minutes for the purpose of an opening statement.

OPENING STATEMENT OF HON. MICHAEL C. BURGESS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS

From last year's 21st Century Cures Act to this year's Food and Drug Administration reauthorization, this subcommittee has been committed to bringing Federal regulation into the modern era of medicine. Today, we continue that work by examining legislation to update the regulatory framework affecting the dissemination of truthful and nonmisleading information about products approved by the Food and Drug Administration.

I practiced medicine for several decades. I know firsthand how challenging it is and how challenging it can be for providers to stay up to the minute with cutting-edge information in both medicine and science. Following the Food and Drug Administration's ap-

proval of a product, the use of that product rapidly evolves based on patient and provider experience. Frequently, the standard of care for a condition is outside of the Food and Drug Administration-approved labeling. Ensuring that healthcare providers have access to new information generated by real-world evidence is critical to optimizing patient care and outcomes. Particularly in medicine, the old adage holds true, knowledge is power.

Our legal framework for the regulation of manufacturer communications sometimes prevents healthcare professionals from receiving the most current scientific information available about the benefits and risks of FDA-approved medicines. A lack of relevant information can lead to physicians making patient care decisions with incomplete information. This is both unfair to the physician and unsafe for the patient.

We owe it to the patient and medical communities to ensure that there is free and full dissemination of truthful and nonmisleading scientific and medical information for healthcare professionals.

I certainly want to thank two of our committee members, the vice chairman of the committee, Brett Guthrie, and Representative Morgan Griffith from Virginia for offering the bills that will be under discussion today. I feel they offer a targeted approach to addressing the problems presented by our regulatory framework for medical product communication. And, if he would like time, I am prepared to yield to the gentleman from Kentucky, if he would like time for an opening statement.

[The prepared statement of Mr. Burgess follows:]

PREPARED STATEMENT OF HON. MICHAEL C. BURGESS

From last year's 21st Century Cures Act, to this year's FDA Reauthorization, this subcommittee has been steadfast in its commitment to bring Federal regulation into the modern era of medicine. Today we will continue that work by examining legislation to update the regulatory framework affecting dissemination of truthful and non-misleading information about FDA-approved products.

I practiced as a physician for several decades, and so I know firsthand how challenging it can be for providers to stay abreast of cutting-edge information in medicine and science. Following FDA-approval of a product, the use of that product rapidly evolves based on patient and provider experience. Frequently the standard of care for a condition is outside of the FDA-approved labeling. Ensuring that healthcare providers are able to access new information generated by real-world evidence is critical to optimizing patient care and outcomes. Particularly in medicine, the old adage holds true—knowledge is power.

Unfortunately, our legal framework for the regulation of manufacturer communication prevents healthcare professionals from receiving the most current scientific information available about the benefits and risks of FDA-approved medicines. A lack of relevant information can lead to physicians making patient care decisions with incomplete information. This is both unfair to the physician and unsafe for the patient.

We owe it to the patient and medical communities to ensure that there is free and full dissemination of truthful and nonmisleading scientific and medical information to healthcare professionals.

I would like to yield the balance of my time to Vice Chairman Guthrie and Representative Griffith to discuss their bills—each of which is a targeted approach to addressing the problems presented by our outdated regulatory framework for medical product communication.

Mr. GUTHRIE. Thank you, Mr. Chairman. There is another very important hearing on opioids going on downstairs, and we have our Kentucky Justice Secretary there.

Mr. Chairman, I want to thank you for holding this hearing today to examine communications between manufacturers and healthcare payers which I addressed in my bill, H.R. 2026, the Pharmaceutical Information Exchange Act. My bill will enable greater information exchange in order to guide health plans, pharmacy benefit managers, and others who develop prescription drug formularies and medical devices to make well-informed decisions about the benefits and costs of medications and medical devices for the populations they cover.

Patients benefit when these formulary decisions are informed by the most recent and reliable scientific evidence on drugs and devices beyond just what we learn from the clinical trials conducted by FDA approval. Our committee has addressed post-approval information exchange. We should take the next logical step by addressing what information can and should be exchanged preapproval by considering the updated discussion draft we are examining today.

I would like to submit for the record a letter of support for my bill by a number of organizations, including the Academy of Managed Care Pharmacy, Humana, Sanofi, and Mayo Clinic.

Mr. BURGESS. Without objection, so ordered.

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

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

Mr. BURGESS. The Chair thanks the gentleman. The Chair would like to recognize the gentleman from Virginia, Mr. Griffith, if he would seek time for an opening statement.

Mr. GRIFFITH. Thank you very much, Mr. Chairman, I do appreciate it. Mr. Guthrie and I were both downstairs introducing former colleagues from the House of Delegates, so we apologize that we came rushing in, but we got that done.

The draft version of my bill that we are discussing today will responsibly set the rules of the road so that manufacturers have the most accurate and up-to-date information about their products that can provide doctors and researchers with that information, and in the appropriate context, to improve patient care and facilitate additional research.

Not only does the lack of clear rules have a public health ramification, but also it has legal consequences. There have been a number of court decisions that raise significant First Amendment questions about the FDA's authority to restrict a drug or device manufacturer from communicating truthful and nonmisleading off-label information about their products.

The Judiciary Branch should not be turned into de facto policy makers because of FDA's misunderstanding of the law or our inaction here in Congress.

I remain open to any and all suggestions from both sides of the aisle and from stakeholders as to how this legislation may be improved, but I am glad we are continuing the dialogue. Also, I also forward to hear from witnesses today about how the FDA's vague policies hinder the facilitation of information to healthcare providers and how this legislation could be a first step in addressing some of the challenges that we will hear about. Thank you. I yield back.

Mr. BURGESS. The gentleman yields back, and the Chair yield back. The Chair recognizes the ranking member of the subcommittee, Mr. Green, 5 minutes for an opening statement, please.

**OPENING STATEMENT OF HON. GENE GREEN, A
REPRESENTATIVE IN CONGRESS FROM THE STATE OF TEXAS**

Mr. GREEN. Thank you, Mr. Chairman. Today, we are considering two draft bills addressing pharmaceutical manufacturer communications on medical products. The Medical Product Communications Act and the Pharmaceutical Information Exchange Act suggest the changes of the rules surrounding the communications from medical product manufacturers will likely have far-reaching implications for decisions made by healthcare providers about which therapies are appropriate for their patients. It is critically important for us to fully consider and appreciate the impact those proposed changes could have on patient safety, health outcomes, and the promotion of value in our healthcare system.

My concern with the two bills we are considering today is that as drafted they would undermine public health, discourage pharmaceutical research, and undermine the FDA's central capacity to ensure medical products used on patients have demonstrated safety and efficiency. Opening the floodgates for off-label communication puts patients at risk, puts a dent in the armor that ensures patients get effective therapies, and not snake oil.

Broadening off-label communications could erode FDA's approval standard as it would enable the uses of products never found to be safe or effective in patients and weaken consumer confidence in the FDA approval process. FDA's approval standard of safety and efficiency is considered to be the gold standard globally. As the FDA Commissioner Dr. Scott Gottlieb has said, the most important incentive to developing useful information remains the ability for companies to market drugs based on what has been proven scientifically. There is an incentive currently for companies to seek FDA's approval for all uses of a drug product if they wish to market the product for those uses and gain coverage for these uses.

Allowing manufacturers to communicate about unproven uses of their products reduces the incentive to go through the FDA's approval process as clinical trials are the most expensive part of the development. Thus, it is not hard to imagine a scenario where a company seeks the narrowest indication for their product, gets on the market, and forgoes on continuing large, well controlled, randomized clinical trials that would prove a product is both safe and effective for broader populations or indications. Patients and doctors should fully be empowered to make joint decisions about their care. This includes the efficiency, risk, and cost of their options.

Information is key, however, and the best decisions are based on accurate, evidence-based information, not just for information that may be incomplete, inconclusive, or at worst inaccurate. The discussion draft of the Medical Product Communications Act would not provide or ensure that patients and care providers have access to better research and evidence. Rather, it would allow drug manufacturers to communicate information about prescription drugs that have not been approved by the FDA. The lack of approval may be

due to contradictory evidence or the lack of any evidence at all, or the need for additional research.

While I have concerns with both discussion drafts as written, I do appreciate that our audience matters. The discussion draft of the Pharmaceutical Information Exchange Act would expand the ability of drug and device manufacturers to communicate healthcare economic information, and scientific information to payers, formularies, technology review committees, or other entities about unapproved uses of products. These audiences are sophisticated and have an inherent interest in being skeptical of claims made outside a product's label. Therefore, it is less problematic in its premise than the other bill we are considering.

While I am willing to work with my colleagues on the proposal, it is critical that these communications promote patient safety, public health, and the appropriate safeguards are in place to avoid damaging unintended consequences. As we consider the issue of off-label communication, we must always keep in mind that the way to truly help patients get the most effective treatments is to maintain the highest standards of safety and evidence and appropriate risk of benefit balance.

Scientifically validated safety and efficiency and the incentives for manufacturers to seek FDA approval are clear and should be preserved. I look forward to hearing from our witnesses and if anybody wants time, I will yield my 45 seconds back. Thank you, Mr. Chairman.

Mr. BURGESS. The gentleman yields back. The Chair thanks the gentleman. The Chair recognizes the gentleman from Oregon, the chairman of the full committee, Mr. Walden, 5 minutes for an opening statement, please.

OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON

Mr. WALDEN. I thank the subcommittee chairman, Chairman Burgess. Thanks for this holding this hearing. It is a really important topic, and it is a topic that has been important for our Members for some time.

Approximately 40 percent, 40 percent of prescriptions in the United States are for indications or uses not included in the FDA-approved product labeling. Although off-label uses of drugs and devices are often the recognized standard of care for treating many conditions, the lack of clarity in the statute and implementing regulations has stifled important information about such uses for being communicated in a responsible and nonpromotional manner by manufacturers.

The FDA has attempted to address this issue, but it has been in a piecemeal fashion over the last 2 decades with various nonbinding guidance documents and policy statements that frankly fall woefully short, particularly given the criminal penalties in play.

As the Supreme Court affirmed in 2011 that First Amendment commercial speech protections extend to medical product manufacturers, every subsequent judicial decision, every decision, has raised significant questions about the extent of FDA's authority to restrict truthful and nonmisleading off-label communications.

So where are we today? The regulators and the courts have spoken. Everyone is left with a vast amount of uncertainty that does nothing to protect or benefit patients. So it is time for Congress to act. And as FDA's authorizing committee, it is our job to clarify this statute and get it right which brings us to this hearing. Neither of these bills are new to my fellow committee members. We discussed an earlier version of both bills during a markup in this subcommittee back in May and we reviewed these updated versions of the full committee markup of the FDA Reauthorization Act last month. Both bills were ultimately withdrawn as amendments to FDARA with a commitment from our colleagues on the other side of the aisle to work with us together to iron out a compromise so we could move these important policies forward and speak as the Congress and not leave this up to a mishmash of court decisions.

So I look forward to continuing that work today.

I believe Morgan Griffith's bill, H.R. 1703, is a serious, well-thought-out policy proposal that responsibly sets the rules of the road in a constitutionally sound manner. I greatly appreciate his willingness to continue to address concerns. He has heard about the legislative language.

I also appreciate Ranking Member Pallone's commitment at the user fee markup to work with us in good faith on this issue through regular order which starts with this important hearing.

In addition, Representative Guthrie's amended version of H.R. 2026 would clarify how drug and medical device companies can share healthcare, economic, or scientific information related to investigational uses of their products with payers and similar entities. These bills do not provide manufacturers with free reign to communicate any and all information about their products. They establish targeted, statutory boundaries within which manufacturers may responsibly disseminate accurate and up-to-date information about medical products. These clarifications will lead to a better informed healthcare system. They will ensure that patients receive high-quality care based on current sound, scientific, and clinical information.

Today, we continue the dialogue. I look forward to a productive discussion and I appreciate the input of our witnesses who are before us today, and with that, unless there are other Members who would like to use the balance of my time, I will yield back the balance of my time.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back. The Chair recognizes the gentleman from New Jersey, the ranking member of the full committee, 5 minutes for an opening statement, please.

[The prepared statement of Mr. Walden follows:]

PREPARED STATEMENT OF HON. GREG WALDEN

Thank you, Chairman Burgess, for holding today's hearing on an increasingly important topic—one that has been a topic amongst our Members for some time.

Approximately 40 percent of prescriptions in this country are for indications or uses not included in the FDA-approved product labeling. Although "off-label" uses of drugs and devices are often the recognized standard of care for treating many conditions, the lack of clarity in the statute and implementing regulations has stifled important information about such uses from being communicated in a responsible, nonpromotional manner by manufacturers.

FDA has attempted to address this issue in a piecemeal fashion over the last two decades with various nonbinding guidance documents and policy statements that fall woefully short, particularly given the criminal penalties in play.

Since the Supreme Court affirmed in 2011 that First Amendment commercial speech protections extend to medical product manufacturers, every subsequent judicial decision has raised significant questions about the extent of FDA's authority to restrict truthful and nonmisleading off-label communications.

So, where are we today? The regulators and the courts have spoken. Everyone is left with a vast amount of uncertainty that does nothing to protect or benefit patients.

It is past time for Congress to act, and as FDA's authorizing committee it is our job to clarify the statute.

Which brings us to this hearing. Neither of these bills are new to my fellow committee members. We discussed an earlier version of both bills during a markup in this subcommittee back in May, and we reviewed these updated versions at the full committee markup of the FDA Reauthorization Act (FDARA) last month.

Both bills were ultimately withdrawn as amendments to FDARA, with a commitment from our Democrat colleagues to continue to work together to iron out a compromise on moving these important policies forward. I look forward to continuing that work today.

I believe Morgan Griffith's bill, H.R. 1703, is a serious, well-thought-out policy proposal that responsibly sets the rules of the road in a constitutionally sound manner. I greatly appreciate his willingness to continue to address concerns he has heard about the legislative language. I am also appreciative of Ranking Member Pallone's commitment at the user fee markup to work with us on this issue through regular order, which starts with this important hearing.

In addition, Rep. Guthrie's amended version of H.R. 2026 would clarify how drug and medical device companies can share healthcare, economic, or scientific information related to investigational uses of their products with payers and similar entities.

These bills do not provide manufacturers with free rein to communicate any and all information about their products. They establish targeted statutory boundaries within which manufacturers may responsibly disseminate accurate, and up-to-date information about medical products. These clarifications will lead to a better-informed health care system and will ensure that patients receive high-quality care based on current, sound scientific and clinical information.

Today we continue the dialogue, and I look forward to a productive discussion.

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

Mr. PALLONE. Thank you, Mr. Chairman. I want to thank you for holding today's hearing. The issue before us today is an important one and I hope that our discussion today will help to inform whether or not it would be appropriate for this committee to take further action.

Today, under current law, medical product manufacturers are required to demonstrate the safety and effectiveness of each intended use of their medical product. This review process has been critical to protecting and promoting public health by ensuring that the benefits of medical products that are prescribed to patients outweigh the risk. It also is common sense. Just because a medical product approved for one use may be found to be safe and effective for that use, doesn't necessarily mean that it will be safe and effective for another use or for another population.

Recognizing that physicians may prescribe treatments off-label in response to individual patient needs, FDA allows the communication of truthful and nonmisleading scientific or medical information regarding unapproved uses of medical products that may assist physicians in making treatment decisions. In those instances, FDA has allowed for manufacturers to respond to requests from physi-

cians about unapproved uses and provide peer reviewed journal articles, scientific or medical texts, and clinical practice guidelines.

Following 21st Century Cures, manufacturers are also now able to share healthcare economic information with payers to help them better understand the economic benefits of an approved treatment.

These are commonsense approaches that allow doctors to address the individual needs of a patient, but also ensure that patients are not unnecessarily exposed to unproven or harmful medical products.

Now today, we are here to examine discussion drafts from Representatives Griffith and Guthrie that would greatly expand the types of scientific information that manufacturers could share without any FDA oversight. While I understand that medical product manufacturers have voiced concerns about their ability to communicate with doctors about their products, I am concerned that these drafts would severely undermine the current protections against marketing unsafe and ineffective medical products.

During this hearing, I hope to hear what materials manufacturers want to share with healthcare professionals and payers that they feel they can't under current law.

The scientific exchange discussion draft would severely restrict the types of evidence the FDA has always relied on to determine the intended use of a medical product. It would also hamstring the Agency from holding bad actors who distribute dangerous drugs or medical devices accountable.

The preapproval communication discussion draft will blow a hole in the current approval process by allowing the communication of any scientific evidence or healthcare economic information to payers or formularies without any recourse to the FDA to prevent bad actors from communicating false or misleading information. Allowing manufacturers to communicate about unapproved products and unapproved uses of their products reduces the incentive of those through FDA's approval process and that is grossly irresponsible in my opinion.

For example, the proposed discussion draft would allow for a manufacturer to publish a biased, scientific study in any medium to constitute scientific exchange. This could simply include posting results of a nonpeer-reviewed study on a company's website, and there is no requirement that this information be truthful.

I am also concerned that these two discussion drafts could expose more patients to medical products that have never been proven to be safe or effective. One study found that 81 percent of medications prescribed for off-label purposes had poor or no scientific support, while another found that patients who received off-label prescriptions were 54 percent more likely to experience an adverse event, as compared to on-label use. And these are risks that we simply cannot ignore.

So Mr. Chairman, if there is a need for greater certainty and clarity on the types of communications that manufacturers are permitted to use under current law, I am willing to have that discussion. However, broadening communication in the way it is proposed under these discussion drafts would, in my opinion, undermine FDA's regulatory review process and the safety and effectiveness approval standard.

I have about a minute. I don't know if anybody wants it. If not, I yield back, Mr. Chairman.

[The prepared statement of Mr. Pallone follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Mr. Chairman, I want to thank you for holding today's hearing. The issue before us today is an important one, and I hope that our discussion will help to inform whether or not it would be appropriate for this committee to take further action at this time.

Today, under current law, medical product manufacturers are required to demonstrate the safety and effectiveness of each intended use of their medical product. This review process has been critical to protecting and promoting public health by ensuring that the benefits of medical products that are prescribed to patients outweigh the risks. It is also commonsense—just because a medical product approved for one use may be found to be safe and effective for that use, does not necessarily mean that it will be safe and effective for another use or for another population.

Recognizing that physicians may prescribe treatments off-label in response to individual patient needs, FDA allows the communication of truthful and nonmisleading scientific or medical information regarding unapproved uses of medical products that may assist physicians in making treatment decisions. In these instances, FDA has allowed for manufacturers to respond to requests from physicians about unapproved uses and provide peer-reviewed journal articles, scientific or medical texts, and clinical practice guidelines. Following 21st Century Cures, manufacturers are also now able to share health care economic information with payors to help them better understand the economic benefits of an approved treatment.

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Today, we are here to examine discussion drafts from Representatives Griffith and Guthrie that would greatly expand the types of scientific information that manufacturers could share without any FDA oversight. While I understand that medical product manufacturers have voiced concern about their ability to communicate with doctors about their products, I am concerned that these drafts would severely undermine the current protections against marketing unsafe and ineffective medical products. During this hearing, I hope to hear what materials manufacturers want to share with health care professionals and payors today that they feel they cannot under current law.

The scientific exchange discussion draft would severely restrict the types of evidence the FDA has always relied on to determine the intended use of a medical product. It would also hamstring the agency from holding bad-actors who distribute dangerous drugs or medical devices accountable.

The preapproval communication discussion draft would blow a hole in the current approval process by allowing the communication of any scientific evidence or health care economic information to payors or formularies without any recourse for the FDA to prevent bad actors from communicating false or misleading information. Allowing manufacturers to communicate about unapproved products and unapproved uses of their products, reduces the incentive to go through FDA's approval process. This is grossly irresponsible.

For example, the proposed discussion draft would allow for a manufacturer to publish a biased scientific study in any medium to constitute "scientific exchange." This could include simply posting results of a nonpeer reviewed study on a company's own website, and there is no requirement that this information be truthful.

I am concerned these two discussion drafts could expose more patients to medical products that have never been proven to be safe or effective. One study found that 81 percent of medications prescribed for off-label purposes had poor or no scientific support, while another found that patients who received off-label prescriptions were 54 percent more likely to experience an adverse event as compared to on-label use. These are risks that we simply cannot ignore.

If there is a need for greater certainty and clarity on the types of communications that manufacturers are permitted to use under current law, I am willing to have that discussion. However, broadening communication in the ways proposed under these discussion drafts would undermine FDA's regulatory review process and the safety and effectiveness approval standard.

Thank you.

Mr. BURGESS. The gentleman yields back. The Chair thanks the gentleman. This concludes Member opening statements, and I would like to remind Members that, pursuant to committee rules, all Members' opening statements will be made part of the record.

And we want to thank our witnesses for being here with us this morning, for taking time to testify before the subcommittee. Each witness will have the opportunity to give a summary of their opening statement, followed by questions from Members.

This morning, we are going to hear from Coleen Klasmeier, a partner of Sidley Austin, LLP; Alta Charo, the Warren Knowles Professor of Law at the University of Wisconsin; Dr. George Van Hare, the Division Chief, Pediatric Cardiology; Louis Larrick Ward, Professor of Pediatrics at Washington University School of Pediatrics; and Co-Director of the St. Louis Children's and Washington University Heart Center; Aaron Kesselheim, Associate Professor of Medicine, Harvard Medical School, Director of Program on Regulation, Therapeutics and Law from the Division of Pharmacoepidemiology and Pharmacoeconomics at the Brigham and Women's Hospital; Linda House, President of the Cancer Support Community; and Katherine Wolf Khachatourian, Vice President, Delegation Oversight, Pharmacy Services of QualchoiceHealth Plan Services.

We appreciate all of you being here today and Ms. Klasmeier, you are recognized for 5 minutes for the purpose of an opening statement. Thank you for being here.

STATEMENTS OF COLEEN KLASMEIER, PARTNER, SIDLEY AUSTIN, LLP; R. ALTA CHARO, WARREN P. KNOWLES PROFESSOR OF LAW, UNIVERSITY OF WISCONSIN; GEORGE VAN HARE, M.D., PRESIDENT, HEART RHYTHM SOCIETY; AARON S. KESSELHEIM, ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL AND BRIGHAM AND WOMEN'S HOSPITAL; LINDA HOUSE, PRESIDENT, CANCER SUPPORT COMMUNITY; AND KATHERINE WOLF KHACHATOURIAN, VICE PRESIDENT, DELEGATION OVERSIGHT, PHARMACY SERVICES, AND STRATEGY, QUALCHOICE HEALTH PLAN SERVICES, INC.

STATEMENT OF COLEEN KLASMEIER

Ms. KLASMEIER. Thank you, Mr. Chairman. Chairman Burgess, Vice Chairman Guthrie, Ranking Member Green, Chairman Walden, members of the subcommittee, my name is Coleen Klasmeier. I am a partner and the head of the FDA Regulatory Practice at Sidley Austin in Washington, DC. I am appearing today on behalf of the Medical Information Working Group.

Today, I would like to make three points. First, FDA's rules governing manufacturer communications are neither clear nor precise. Decisions to prescribe and use lawfully marketed drugs and medical devices in ways that differ from the FDA authorized labeling, so-called off-label use, are a constituent part of medical and surgical practice and can also be the standard of care. FDA has long recognized the need for prescribers to receive and for manufacturers to have some ability to provide information outside of product labeling to help support clinical decision making. As a result, al-

though a manufacturer is prohibited from promoting its product for new uses, it can lawfully provide information about off-label uses within defined circumstances.

Currently, there are four safe harbors. Only one is set forth in a binding regulation. The others are in nonbinding documents. They therefore lack the force of law. Moreover, two of the four safe harbors have been the subject of ongoing FDA proceedings since 2011. Under these policies, a manufacturer can provide off-label information ostensibly without fear of enforcement in four scenarios involving scientific exchange, responses to unsolicited requests, continuing education, and reprints of journal articles, reference texts, and clinical practice guidelines. Each safe harbor is subject to a number of qualifying criteria and additional requirements which are unclear in many key respects.

Moreover, FDA has been unable to complete its process of revising the safe harbor policies, so questions frequently arise regarding the relationship between the old policies and the new policies.

In addition, there is a lack of symmetry between the safe harbors that apply to drugs and those that apply to medical devices. In short, the safe harbors are a mess. As a result, manufacturers cannot confidently rely on the safe harbors and that has public health consequences. For example, it is common for the Advisory Committee on Immunization Practices, a Federal statutory advisory committee to the CDC, to make recommendations for vaccines that are arguably off-label. ACIP recommendations might vary the dosing schedule or recommend use of a vaccine in a new patient population. The vaccine manufacturer would reasonably fear that communicating about the ACIP recommendation to physicians or payers could be characterized by Government as unlawful, off-label promotion. Ultimately, the public health would not be advanced because physicians would not receive manufacturer communications reinforcing that recommendation.

The regulatory scheme also has legal consequences. The First Amendment case law makes clear that FDA is limited in its power to prohibit drug and device manufacturers from engaging in accurate communications about their product. FDA's regulatory scheme also implicates the due process laws of the Fifth Amendment which requires Government agencies to establish rules that are clear and to give fair notice of what is prohibited, particularly in the context of free expression.

Second, the existing FDA regulatory scheme for manufacturer communication is highly unstable. The lack of clear rules to allow manufacturers an appropriate measure of latitude to communicate about their products is only a part of the problem. FDA and the Justice Department impose aggressive restraints on manufacturers' speech. Although manufacturers have indeed settled many cases involving off-label promotion allegations in recent years, in some instances individuals and firms have raised First Amendment arguments in court and those arguments have succeeded. FDA's regulatory scheme continues to burden constitutionally protected speech and is therefore at risk from additional lawsuits.

The Medical Information Working Group has for more than 10 years and across more than 20 submissions, requested targeted clarifications to the existing FDA safe harbors and to key statutory

terms such as labeling and intended use. We have not asked for and we do not want a healthcare system in which manufacturers can market their product based on spurious or unsubstantiated claims of safety or efficacy.

Third, legislation could dramatically improve the regulatory scheme. Although the MIWG has been dedicated to direct engagement with FDA on manufacturer communication issues since 2006, we also recognize the paramount role of Congress and we believe that legislation may be necessary for several reasons.

For one thing, FDA action has been slow and ineffectual. It has been almost 6 years, for example, since FDA published a notice in the Federal Register asking for comment on scientific exchange and responses to unsolicited requests. Where FDA has taken action, the policy has tacked in the wrong direction becoming less clear and even more speech restrictive. For these reasons, it would be helpful for Congress to step in and set the overall policy direction for FDA to implement.

Legislation is also more durable than unilateral FDA action. Statutory law is not subject to the same variability as agency pronouncements and cannot be undone in a future administration. Legislation would be less susceptible to legal challenge than a regulation or an FDA guidance document. Regulations have the force of law, but the Administrative Procedure Act creates a vehicle for challenge in court, whereas a statutory change could only be challenged successfully in court on constitutional grounds.

Legislation may also be necessary given the likelihood of continued judicial involvement in this area. Although we value the contributions that recent judicial decisions have made to the body of relevant law, we also believe that litigation is not the best way to make law on important public health issues where there is little room for error. We are especially concerned that some future lawsuit might eviscerate the FDA regulatory scheme.

We see great value in congressional engagement with FDA on manufacturer communication issues to help assure the regulatory scheme is put on to a more stable and sustainable footing. Thank you very much for the opportunity to testify today and I look forward to your questions.

[The prepared statement of Ms. Klasmeier follows:]

Testimony of Coleen Klasmeier on Behalf of the Medical Information Working Group
One-Page Summary

1. FDA's rules governing manufacturer communications are neither clear nor precise.

FDA has established four "safe harbor" policies recognizing the public health value of manufacturer dissemination of accurate information relating to off-label uses. Each safe harbor is subject to a number of vague qualifying criteria and burdensome additional requirements. The policies are also hard to follow because FDA has started but failed to complete proceedings to revise the safe harbor policies, and not all of the policies apply clearly to both drugs and medical devices. The lack of clarity corresponds to under-utilization of the safe harbors, which reduces clinically valuable manufacturer communication, undermines optimal patient care, and presents First and Fifth Amendment issues.

2. The existing FDA regulatory scheme for manufacturer communications is unstable.

FDA and the Department of Justice aggressively pursue enforcement actions with respect to "off-label" speech, but First Amendment arguments in those cases have been accepted by reviewing courts. Litigation has a destabilizing effect on the regulatory scheme and threatens FDA's ability to make incremental changes. The public health and legal consequences of the developing case law point up the need for modifications to the existing rules and policies.

3. Legislation could dramatically improve the regulatory scheme.

Legislation could be helpful in addressing FDA's seeming inability to make meaningful progress in reviewing and modifying the rules and policies governing manufacturer speech. Legislation could also stabilize the existing system in a more durable manner than regulations, which can be reversed through agency action or more easily invalidated through litigation. Legislation could also address the risk of a frontal assault on FDA regulation.

**“Examining Medical Product Manufacturer Communications”
Wednesday, July 12, 2017
Committee on Energy and Commerce
Subcommittee on Health**

Testimony of Coleen Klasmeier on Behalf of the Medical Information Working Group

Good morning. I am Coleen Klasmeier, a partner and head of the FDA regulatory practice at the law firm Sidley Austin in Washington, DC. I am appearing today on behalf of the Medical Information Working Group. The MIWG is an informal working group of manufacturers of biopharmaceutical products and medical devices, formed in 2006 to seek clarity in the enforcement and regulatory environment affecting communications about investigational and lawfully marketed medical products. Although we have been involved in a variety of efforts on these issues, from educational outreach to amicus briefs and submissions to federal agencies, the bulk of our work in recent years has involved FDA. We have made twenty submissions to FDA on manufacturer communications since 2008.¹ Today I would like to make three points.

1. FDA’s rules governing manufacturer communications are neither clear nor precise.

Decisions to prescribe and use lawfully marketed drugs and medical devices in ways that differ from the FDA-authorized labeling—“off-label use”—are a constituent part of medical and surgical practice, and can also be the standard of care.² FDA has long recognized the need for prescribers to receive, and manufacturers to have some ability to share, information outside of

¹ The MIWG’s submissions to FDA are available at www.miwg.org and www.regulations.gov.

² See, e.g., FDA Draft Guidance, Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices (Dec. 2011) (“FDA recognizes that these off-label uses or treatment regimens may be important therapeutic options and may even constitute a medically recognized standard of care.”).

product labeling to help support clinical decision-making.³ As a result, although a manufacturer is prohibited from “promoting” its product for “new uses,” it can lawfully provide information about off-label uses within defined circumstances. Currently there are four “safe harbors.” Only one is set forth in a binding regulation; the others are in non-binding documents.⁴ They therefore lack the force of law. Moreover, two of the four safe harbors have been the subject of ongoing FDA proceedings since 2011.

Under these policies, a manufacturer is ostensibly permitted to provide off-label use information without fear of enforcement in four sets of circumstances, involving (1) “scientific exchange,” (2) responses to unsolicited requests, (3) continuing education, and (4) reprints of certain journal articles, reference texts, and clinical practice guidelines. Each safe harbor is subject to a number of qualifying criteria and additional requirements which are unclear in many respects. Moreover, FDA has been unable to complete its process of revising the safe harbor policies, so questions frequently arise regarding the status of the old policies relative to

³ See, e.g., 59 Fed. Reg. 59,820, 59,822-23 (Nov. 18, 1994) (recognizing “the importance of dissemination of reliable scientific information on both approved and unapproved uses,” and describing “a number of policies” that permit manufacturer dissemination of information on “unapproved uses”); 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972) (FDA “is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.”) (emphasis added).

⁴ See 21 C.F.R. § 312.7 (scientific exchange, for drugs); 59 Fed. Reg. at 59,823 (unsolicited requests); 62 Fed. Reg. 64,093 (Dec. 3, 1997) (continuing education and similar activities); FDA Guidance, Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices (Jan. 2009) (reprints).

the proposed new policies.⁵ In addition, there is a lack of symmetry between the policies for drugs and those for devices.⁶ In short, the safe harbors are a mess.

As a result, manufacturers cannot confidently rely on the safe harbors, and that has public health consequences. For example, it is common for the Advisory Committee on Immunization Practices—a statutory advisory committee to the CDC—to make recommendations for vaccines that are arguably “off-label.”⁷ An ACIP recommendation might vary the dosing frequency for a vaccine, for example. Under FDA rules, the vaccine manufacturer would be prohibited from promoting the vaccine in accordance with the ACIP recommendation. Moreover, its ability to engage in non-promotional, “safe harbored” communications about the ACIP recommendation would be significantly frustrated by the lack of clarity in the safe harbors, and in particular, the fear that communicating about the ACIP recommendation could be characterized by the government as unlawful off-label promotion. Ultimately, the public health benefits of the ACIP recommendation would not be advanced fully

⁵ For example, in December 2011, FDA launched a process to revise the “scientific exchange” and “unsolicited requests” safe harbor policies. The status of these efforts remains unclear. *See* 76 Fed. Reg. 81,508 (Dec. 28, 2011); 76 Fed. Reg. 82,303 (Dec. 30, 2011). FDA published a revised draft guidance on reprints, but the draft has not been finalized. FDA Guidance, Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices (Revised Draft Guidance) (Feb. 2014). In June 2014, FDA granted two citizen petitions filed by the MIWG, stating that the agency planned to issue guidance addressing “distributing scientific and medical information on unapproved new uses . . . and manufacturer discussions regarding scientific information more generally, by the end of the calendar year.” Letter from Leslie Kux, Assistant Commissioner for Policy, FDA to MIWG Counsel, Docket Nos. FDA-2011-P-0512 and FDA-2013-P-1079 (June 6, 2014).

⁶ For drugs, the “scientific exchange” safe harbor is codified at 21 C.F.R. § 312.7. The analogous regulation for medical devices, 21 C.F.R. § 812.7, omits the safe harbor language.

⁷ *See, e.g.*, Morbidity and Mortality Weekly Report 2013; 62(RR04);1-34, available at https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6204a1.htm?s_cid=rr6204a1_w (recommending MMR vaccination for infants aged ≥ 6 months who plan to travel or live abroad).

because the intended audience for the recommendation would not receive manufacturer communications reinforcing the advisory committee's findings or advice.

The regulatory scheme likewise has legal consequences. The First Amendment case law makes clear that FDA is limited in its power to prohibit drug and medical device manufacturers from communicating about their products. The familiar Central Hudson test for commercial speech holds that accurate speech about lawful activity—and off-label use is, with very limited exceptions, lawful activity—is subject to constitutional protection.⁸ That means the government, in defending regulations that burden that speech, must demonstrate that those regulations are premised on a substantial government interest.⁹ In addition, the government must prove that its regulations directly advance that interest, and that the regulations are sufficiently tailored to the interest.¹⁰ More recently, the Supreme Court used a “heightened” scrutiny test in a case involving a state law restricting accurate manufacturer speech about prescription drugs, suggesting that the Central Hudson test for evaluating commercial speech regulation might not be protective enough of the speech.¹¹ The constitutional test for government regulation of scientific speech,¹² or “mixed” speech (communication that

⁸ Central Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n, 447 U.S. 557 (1980).

⁹ *Id.* at 564 (“The State must assert a substantial interest to be achieved by restrictions on commercial speech.”).

¹⁰ *Id.* (“First, the restriction must directly advance the state interest involved; the regulation may not be sustained if it provides only ineffective or remote support for the government's purpose. Second, if the governmental interest could be served as well by a more limited restriction on commercial speech, the excessive restrictions cannot survive.”).

¹¹ Sorrell v. IMS Health Inc., 564 U.S. 552, 565 (2011).

¹² Miller v. California, 413 U.S. 15, 34 (1973); Keyishian v. Bd. of Regents, 385 U.S. 589, 603 (1967); Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 62 (D.D.C. 1998); Bd. of Trs. v. Sullivan, 773 F. Supp. 472, 474 (D.D.C. 1991).

inextricably combines scientific and commercial speech), is the even more demanding “strict scrutiny” test, and FDA regulations affecting those two species of communication would almost certainly be invalidated by a court.¹³

FDA’s regulatory scheme also implicates the Due Process Clause of the Fifth Amendment, which requires government agencies to establish clear rules that give fair notice of what is prohibited.¹⁴ The adoption of clear, binding rules is essential to bring FDA’s regulatory scheme into alignment with the Fifth Amendment.

2. The existing FDA regulatory scheme for manufacturer communications is unstable.

The lack of clear rules that allow manufacturers an appropriate measure of latitude to provide accurate information about their products is only part of the problem. FDA—and in important respects the Department of Justice, which represents FDA in court and brings its own investigations under the Federal Food, Drug, and Cosmetic Act, the False Claims Act, and other statutes—imposes aggressive restraints on manufacturer speech. Although manufacturers have settled many cases involving “off-label promotion” allegations in recent years, in some instances individuals and firms have raised First Amendment arguments in court, and those arguments have succeeded.¹⁵ Arguably the most famous example involves the Caronia case,

¹³ Riley v. Nat’l Fed., 487 U.S. 781, 796 (1988) (“Thus, where, as here, the component parts of a single speech are inextricably intertwined, we cannot parcel out the speech, applying one test to one phrase and another test to another phrase. Such an endeavor would be both artificial and impractical. Therefore, we apply our test for fully protected expression.”).

¹⁴ FCC v. Fox Television Stations, Inc., 132 S. Ct. 2307, 2318 (2012) (quoting United States v. Williams, 553 U.S. 285, 304 (2008)).

¹⁵ But see United States v. Harkonen, 510 F. App’x 633 (9th Cir. 2013), cert. denied, 134 S. Ct. 824 (2014).

invalidating a conspiracy conviction on First Amendment grounds.¹⁶ The Amarin case involved a manufacturer's assertion that its product could be marketed with out-of-label efficacy claims that FDA had found accurate but nevertheless sought to prohibit.¹⁷ In Pacira, FDA had granted approval for a prescription analgesic drug but later sought to prohibit the company from promoting the product according to its labeled indication.¹⁸ This string of decisions has led some observers to decry judicial involvement in adjudicating drug efficacy claims.¹⁹ In some cases, observers have gone further, claiming that the First Amendment case law is "incompatible with regulating drug promotion."²⁰

But maintaining the status quo ignores the law and harms the public health. FDA's regulatory scheme is at risk from additional lawsuits because, despite some incremental improvements, the rules continue to burden constitutionally protected speech. Keeping things as they are also ignores the Fifth Amendment requirements for clear, prospectively defined rules. The First and Fifth Amendments represent the principle that the public health is advanced by more, rather than less, accurate information to inform clinical decision making. Observers who seek to set the Constitution on a collision course with their own ideas about

¹⁶ United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).

¹⁷ Amarin Pharma, Inc. v. FDA, 119 F. Supp. 3d 196 (S.D.N.Y. 2015).

¹⁸ Stipulation and Order at 2, Pacira Pharms., Inc. v. FDA, No. 15-7055 (S.D.N.Y. Dec. 14, 2015), ECF No. 45.

¹⁹ Joshua M. Sharfstein & Alta Charo, The Promotion of Medical Products in the 21st Century: Off-label Marketing and First Amendment Concerns, JAMA (published online Sept. 14, 2015).

²⁰ Aaron S. Kesselheim, Michelle M. Mello, and Jerry Avorn, FDA Regulation of Off-Label Drug Promotion Under Attack, 309 JAMA 445 (2013).

public health policy ignore the idea that free speech itself protects and promotes the public health.

To be clear, the MIWG does not support any reform measure that would take FDA out of its current role in reviewing claims of drug and device effect in advance. The measures we have requested involve targeted clarifications to the safe harbors and key statutory terms such as “labeling” and “intended use.” The MIWG has not sought dramatic changes to the regulatory scheme that would open the floodgates to off-label promotion. We have not asked for, and do not want, a health care system in which manufacturers can market their drugs and medical devices based on spurious or unsubstantiated claims of clinical utility. We have asked, instead, for clear rules that distinguish permitted from prohibited communications, and that provide manufacturers with reasonable latitude to communicate about their products.

3. Legislation could dramatically improve the regulatory scheme.

Although the MIWG has been dedicated to direct engagement with FDA on manufacturer communication issues, we recognize the paramount role of Congress and we believe that legislation may be necessary, for several reasons.

FDA action has been slow and ineffectual. It has been almost six years, for example, since FDA published a notice in the Federal Register soliciting public comment on the scope of the scientific exchange safe harbor and on a new draft guidance on unsolicited requests.²¹ Where FDA has taken action, the policy has tacked in the wrong direction, becoming less clear

²¹ See 76 Fed. Reg. 81,508 (Dec. 28, 2011); 76 Fed. Reg. 82,303 (Dec. 30, 2011).

and more speech restrictive.²² It appears FDA has been hamstrung by differing views internally and with the Department of Health and Human Services.²³ FDA officials might also be reluctant to do or say anything publicly that they believe would help tee up more litigation that they might not win.

For these reasons, it would be helpful for Congress to step in and set the overall policy and direction for FDA to implement. We believe that Section 3037 of the 21st Century Cures legislation, the so-called FDAMA 114 fix—is a paradigmatic example. There, Congress established a clear rule, and FDA promptly executed that rule through a reasonably clear and speech-enabling guidance document.²⁴

Legislation is more durable than unilateral FDA action. Statutory law is not subject to the same variability as agency pronouncements, and cannot be undone by agency leadership in a future Administration. Legislation would also be less susceptible to legal challenge than a regulation or a guidance document. Regulations have the force of law, but the Administrative Procedure Act creates a vehicle for challenge, whereas a statutory change could only be challenged successfully on constitutional grounds.

²² The new draft guidance on unsolicited requests includes six pages of criteria for determining whether speech qualifies for the safe harbor. The earlier iteration of the policy, published in 1994, comprised a single paragraph.

²³ Sources: FDA, HHS Leaders Clash On Off-Label Communication Next Steps, Inside Health Policy (Jan. 22, 2016), available at <https://insidehealthpolicy.com/daily-news/sources-fda-hhs-leaders-clash-label-communication-next-steps>.

²⁴ The amended provision is codified at 21 U.S.C. § 352(a). See FDA Guidance, Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers (Draft) (Jan. 2017), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537347.pdf>.

Legislation may be necessary given the likelihood of continued judicial involvement.

Although we value the contributions that recent judicial decisions have made to the body of relevant constitutional and regulatory law, we also believe that litigation is not the ideal method of making law on issues that leave little room for error. We are particularly concerned by the possibility of a broadside attack on the FDA regulatory scheme that could result in the entry of a judicial order with significant and far-reaching consequences for the entire regulatory framework, including the agency's ability to enforce premarket review requirements.

We greatly appreciate the opportunity that this subcommittee had created for discussion of these important issues today. Thank you once again, and I look forward to your questions.

Mr. BURGESS. I thank the gentlelady for her testimony.
 Ms. Charo, you are recognized for 5 minutes, please.

STATEMENT OF R. ALTA CHARO

Ms. CHARO. Chairman Burgess, Vice Chairman Guthrie, Congressman Green, and members of the committee, thank you for the opportunity to address you on issues surrounding communication and marketing of off-label uses.

My name is Alta Charo. I am the Warren P. Knowles Professor of Law at the University of Wisconsin. I am an elected member of National Academy of Medicine, formerly known as the Institute of Medicine, where I have served on a number of committees including the one that produced a report on ensuring the safety of the U.S. drug system. I also served as an advisor in the Office of the Commissioner at FDA from 2009 to 2011, but I would like to note for the record that I speak for myself only and not for FDA and not for the National Academies.

There are two possible reasons to expand communication about off-label uses. One is to ensure that the law is consistent with the requirements of the First Amendment. The other is to protect public health by increasing patient access to safe and effective drugs. And I share those two goals. I don't, however, believe that the two amendments under discussion are necessary to achieve those goals. Indeed, I fear the unintended consequence of adopting the language in these amendments would be to undermine public health, to discourage pharmaceutical research, and to set pharmaceutical regulation back by more than 100 years.

As noted in an article I co-authored with Josh Sharfstein, formerly the principal deputy at FDA, our drug regulation system has prohibited false or misleading advertising since 1906. And in 1962, broad marketing for secondary uses of thalidomide caused thousands of severe birth defects worldwide, and Congress then recognized that a product can be "safe and effective" for one intended use where the benefits exceed the risks, but not "safe and effective" for another which why approval of a drug for a labeled indication does not mean it will be safe and effective for off-label uses and precisely why additional studies are needed.

This requirement to demonstrate safety and effectiveness for an intended use applies both to the first approval of a new compound or a new drug, as well as to any supplemental indication. And while it is true there have been a handful of cases narrowing constraints on commercial speech regarding unapproved "off-label" uses, the courts have consistently upheld commercial speech restriction with respect to the first approval of a new product. If the First Amendment means that off-label promotion must be permitted, then promotion of entirely untested, never-approved drugs should also garner the same protection. In both cases, the majority of drugs will fail to show that they are safe and effective when the testing has been completed and the substantial public interest in achieving that certainty is the same regardless of whether it is an entirely new drug or a supplemental indication for an existing drug.

If we were to eliminate the restrictions on commercial speech for entirely unapproved drugs, it would return us to the 1906 law

where prosecution for false and misleading marketing took place only after people had been harmed.

Scientific journals and conferences are already allowed to present information about off-label uses. Sponsors can answer questions from physicians and provide reprints of peer-reviewed articles, even if related to off-label uses. And in April 2017, the FDA further clarified these rules and used guidances as a more flexible mechanism to provide that information. Legislation, regulation, and court decisions have not the kind of flexibility that guidances have. We have entered an era in which communication takes on many new forms ranging from tweets to Facebook to any number of internet sources and it is important to maintain flexibility in how we regard communication and its influence and its intended purpose, rather than solidifying it in legislation which can be difficult to change over time.

Now the proposed amendment of Section 201 muddies the exceptions that FDA has outlined and I fear it risks eviscerating the general rule against off-label promotion even if that is not its intent. It also has the effect of immunizing sponsors from responsibility even if they know and take advantage of the now blurry line between legitimate scientific exchange and illegal marketing.

The proposed amendment of Section 502, I fear, will exacerbate this problem, by allowing premature information to be delivered to formularies and payers with the probable effect of increasing patient use of unproven and unsafe therapies. And as has been noted already by Members here on the committee, studies have repeatedly shown that even products that look promising in early trials will usually be shown to be unsafe or ineffective when larger trials are completed. And indeed, overall only about one in five compounds, only one in five, will successfully move from Phase 2 to Phase 3 trial, with lack of efficacy as the most common reason for failure.

In a series of articles recently produced by Professor Christopher Robinson at the University of Arizona, we can also see that multiple studies show that the majority of off-label uses also will turn out to be either unsafe or ineffective. Encouraging coverage before approval is to encourage expanded use before approval of treatments that we now know empirically are likely to fail. And I fear that the effect would be to increase use that will harm more patients than it helps.

History amply demonstrates there is a compelling public interest in unbiased evaluation of evidence; in clear, accurate communication; in maintaining incentives for research. The combined effect of these amendments is to expand promotion and payment for unproven uses of drugs. It undercuts the marketing advantages that the law now uses as an incentive for sponsors to complete the research needed to see which uses are, in fact, safe and effective. And in turn, it leaves physicians, patients, formularies, and payers without independently verified information. For complex products like drugs, the marketplace of ideas cannot work properly with unvetted information from necessarily self-interested sources. And when using the wrong drug can injure patients or cause them to miss out on effective treatment, it is an invitation to another tragedy when we prevent FDA from doing its job to protect the public.

Thank you very much.
[The prepared statement of Ms. Charo follows:]

Testimony of R. Alta Charo
before the Subcommittee on Health
Energy & Commerce Committee of the U.S. House of Representatives
12 July 2017

Chairman Burgess, Vice-Chairman Guthrie, Congressman Green, members of the committee, thank you for this opportunity to address you on issues surrounding communication and marketing of medical products for off-label uses. My name is Alta Charo. I am the Warren P. Knowles Professor of Law at the University of Wisconsin, and an elected member of the National Academy of Medicine (formerly known as the IOM), where I have served on a number of committees, including one that examined the system for ensuring drug safety. I also served as an advisor in the Office of the Commissioner at FDA from 2009 to 2011. I would note for the record that I am not here to represent either the National Academies or the FDA, and that the opinions I express here are my own.

There are two possible reasons to expand communication about off-label uses. One is to ensure the law is consistent with the free speech protections of the First Amendment. The other is to promote public health by increasing patient access to safe and effective drugs. I share these goals, but do not find that the two amendments under discussion today are needed. Indeed, the unintended consequence of adopting this language would be to undermine public health, discourage pharmaceutical research, and set pharmaceutical regulation back by more than 100 years.

As noted in an article I co-authored with Josh Sharfstein,¹ formerly the principal deputy commissioner at FDA, our drug regulation system has prohibited false or misleading advertising since 1906. In 1962, when broad marketing for secondary uses of thalidomide caused thousands of severe birth defects worldwide, Congress recognized that a product can be “safe and effective” for one intended use where the benefits exceed the risks, but not “safe and effective” for another. This is why approval of a drug for a labeled indication does not mean it will be safe and effective for off-label uses, and why additional studies are needed to explore them.

This requirement to demonstrate safety and effectiveness for an intended use applies to both the first approval of a new drug and to any approval of a supplemental indication. Despite a handful of cases narrowing constraints on commercial speech regarding unapproved “off-label” uses, courts have consistently upheld commercial speech restriction with respect to the first product approval. If the First Amendment means that off-label promotion must be permitted, then promotion of entirely untested, unapproved drugs should also garner the same

¹ Sharfstein and Charo, “The Promotion of Medical Products in the 21st Century: Off-label Marketing and First Amendment Concerns,” JAMA. 2015;314(17):1795-1796.

protection. But this would return us to the 1906 law, where prosecution for false and misleading marketing took place only after people had been harmed.

Scientific journals and conferences are already allowed to present information about off-label uses. Sponsors can answer questions from physicians and provide reprints of peer-reviewed articles, even if related to off-label uses. The proposed amendment of Section 201 muddies these exceptions, and risks eviscerating the general rule against off-label promotion. It also immunizes sponsors from responsibility, even if they know and take advantage of the now blurry line between legitimate scientific exchange and illegal marketing.

The proposed amendment of Section 502 exacerbates this problem, by allowing premature information to be delivered to formularies and payors, with the probable effect of increasing patient use of unproven or unsafe therapies. Studies have repeatedly shown that even products that look promising in early trials will usually be shown to be unsafe or ineffective when larger trials are completed. Indeed, overall only about 1 in 5 compounds successfully move from Phase 2 to Phase 3 trial,² with lack of efficacy as the most common reason for failure.³ And as noted by University of Arizona professor Christopher Robinson, multiple studies show that the majority of off-label uses also turn out to be either unsafe or ineffective,⁴ and increasing use without proper research will harm more patients than it helps.

History amply demonstrates that there is compelling public interest in unbiased evaluation of evidence; in clear, accurate communication; and in maintaining incentives for research. The combined effect of these amendments is to expand promotion and payment for unproven uses of drugs. It undercuts the marketing advantages that the law uses as an incentive for sponsors to complete the research needed to see which uses are in fact safe and effective. In turn, it leaves physicians, patients, formularies and payors without independently verified information. For complex products like drugs, the marketplace of ideas cannot work properly with un-vetted information from a self-interested source. And when using the wrong drug can injure patients or cause them to miss out on effective treatment, it is an invitation to another tragedy when we prevent FDA from doing its job to protect the public.

Thank you for your attention.

² 2015 CMR International Pharmaceutical R&D Executive Summary
(http://cmr.clarivate.com/pdf/Executive_Summary_Final.pdf)

³ Harrison, "Phase II and phase III failures: 2013–2015," NATURE REVIEWS DRUG DISCOVERY 15, 817–818 (2016) [Published online 04 November 2016].

⁴ Arizona Legal Studies Discussion Paper No. 16-19, "The Tip of the Iceberg: A First Amendment Right to Promote Drugs Off-Label," by Christopher Robertson June 2017 (citing Tewodros Eguale et al., "Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population," 176 JAMA INTERN MED. 55-63 (Jan. 2016) and David Radley, Stanley Finkelstein, & Randall Stafford, "Off-Label Prescribing Among Office-Based Physicians," 166 ARCH. INT. MED. 1021 (2006).

Mr. BURGESS. The Chair thanks the gentlelady.

The Chair recognizes Dr. Van Hare, 5 minutes for your opening statement, please.

STATEMENT OF GEORGE VAN HARE

Dr. VAN HARE. Good morning, Chairman Burgess, Ranking Member Green, and members of the subcommittee. Thank you for holding this hearing and for inviting me to testify on this important topic. My name is George Van Hare. I am Chief of Pediatric Cardiology at St. Louis Children's Hospital in St. Louis, Missouri. My clinical practice is focused on caring for children with heart rhythm disorders. This year I have the honor of serving as the president of the Heart Rhythm Society. The Heart Rhythm Society is the international leader in science, education, and advocacy for cardiac arrhythmia professionals. Its members include 6,100 physicians, scientists, nurses, and other allied health professionals in more than 90 countries.

Sharing comprehensive, scientifically valid data is critical to the practice of medicine generally, and it is even more critical for particular specialties. It is sometimes claimed that the use of drugs or devices off-label is the result of a choice by physicians. Sometimes this is

true. However, for pediatric sub-specialists, this is usually not the case. This is due to the fact that very few of the medications for arrhythmias that are on the market are formally approved for use in children. Thus, using treatments off-label is often our main method of

treatment of children. Similarly, catheters that we use for catheter ablation procedures are labeled for a limited number of specific arrhythmias, but are used for treating and curing all types of arrhythmias in adults and children.

By way of example, I would like to cite the specific drug, amiodarone, brand name Cordarone. This is one of our most important medications for the treatment of potentially life-threatening arrhythmias, particularly in patients who have undergone successful surgical repair of complex

congenital heart defects. The FDA-approved label simply states "The safety and efficacy of Cordarone Tablets in pediatric patients have not been established." This means that the manufacturer is not allowed to share prospectively any data that they may have concerning experience with this drug in children.

Another example, not specific to children, is a labeling of ablation catheters. These devices are used in performing catheterization procedures to cure arrhythmias. In the last 25 years, these procedures have essentially replaced open heart surgery as the best option for a curative procedure. Their labeling is limited to only certain arrhythmias. For example, the Cryocath, a cryoablation catheter manufactured by Medtronic, is only labeled for treating one common arrhythmia, AVNRT, despite the fact that it is ideal for treating other, more dangerous arrhythmias. It would be absurd to use a different catheter for these other arrhythmias on the basis of the labeling, and even more absurd if you consider open heart surgery. However, because of the labeling, technical support representatives of the manufacturer are not allowed to discuss other

indications directions and prospectively, despite the fact that the use of this catheter for these other indication sis widely agreed to be the standard of care.

There is an important way in which information sharing among physicians may also be adversely affected. When a medical conference is directly sponsored by a manufacturer, these conferences do not qualify as official continuing medical education events. Consequently, physician speakers are considered to be “agents” of the manufacturer sponsoring the event, and they are also limited to discussing only the labeled indications. Any discussion between physicians regarding experiences with drugs or devices that are off-label at such events must occur informally, rather than as part of the program, and thus these discussions do not benefit from the great potential for information sharing among physician attendees.

The good news is that it doesn’t have to be this way. It is likely that there is a large amount of data maintained by manufacturers, which under the current rules they are not allowed to proactively share with clinicians. I urge the committee to explore ways to define acceptable types of real-world evidence that manufacturers might proactively share with medical decision makers. These types of data might include observational studies, pharmacokinetic studies, and information on particular sub-populations. The data must be truthful, presented in context, and scientifically valid.

There is some concern that manufacturers might overwhelm physicians with data taken out of context or data that are misleading and skewed to present a more favorable picture than is realistic. However, physicians are trained to analyze data. We know how to evaluate the validity of studies. If regulatory restrictions provide guard rails to ensure that data are truthful and presented in context, physicians are fully capable of analyzing such data effectively.

In my opinion, a reasonable regulatory paradigm lies somewhere between no communication and completely unrestricted communication. The current structure is not optimal for fostering the advancement of medical knowledge, and it leaves many patients and their physicians at an unnecessary disadvantage. Additionally, it seems incongruous to me that the manufacturer, the entity with the most robust data related to a product, cannot share information they hold proactively while any lay person with an internet connection can freely disseminate whatever information they like about that same product however biased and unreliable.

In closing, I hope that my testimony has provided the committee with a real-world perspective on how the current rules often prevent physicians from receiving valuable, clinical information in a timely fashion. I respectfully suggest that Congress should establish ways to unlock

data maintained by manufacturers related to off-label use of drugs and devices. I thank the committee for its time. The Heart Rhythm Society would welcome the opportunity to work with you on policy proposals related to this topic. Thank you.

[The prepared statement of Dr. Van Hare follows:]

**TESTIMONY OF DR. GEORGE VAN HARE, MD, FHRS, CCDS, CEPS-PC
PRESIDENT, HEART RHYTHM SOCIETY**

Before the

U.S. HOUSE OF REPRESENTATIVES
ENERGY AND COMMERCE COMMITTEE
SUBCOMMITTEE ON HEALTH

Hearing entitled:

“Examining Medical Product Manufacturer Communications”

July 12, 2017

Chairman Burgess, Ranking Member Green, and Members of the Subcommittee: thank you for holding this hearing and for inviting me to testify on this important topic. My name is George Van Hare. I am Chief of Pediatric Cardiology at Saint Louis Children's Hospital and Professor of Pediatrics at Washington University School of Medicine in St. Louis, Missouri. My clinical practice is focused on caring for children with heart rhythm disorders, as well as adults who are survivors of surgery for congenital heart disease. As such, I prescribe antiarrhythmic medications, utilize medical devices such as catheters for cardiac ablation procedures, and implant pacemakers and defibrillators. This year, I have the honor of serving as the President of the Heart Rhythm Society. Founded in 1979, the Heart Rhythm Society is the international leader in science, education and advocacy for cardiac arrhythmia professionals. Its members include 6,100 physicians, scientists, nurses and other allied health professionals in more than 90 countries who specialize in electrophysiology and perform basic, clinical, and translational research science. Electrophysiology is a distinct subspecialty of cardiology, and adult electrophysiologists are board certified through the American Board of Internal Medicine.

BACKGROUND: OFF-LABEL USE

The Food and Drug Administration (FDA) approves drugs and medical devices for specific indications, which are reflected in the product's label. Off-label use refers to the utilization of an FDA-approved treatment or device for any use other than the one(s) listed in the approved labelling, or in a population not reflected in the labelling, such as children. It is important to note that these off-label uses are often not experimental uses. In fact, some are so common they have become the standard of care. Many off-label uses are well-documented in the peer-reviewed

literature, are discussed widely among physicians, and are cited as standard and accepted treatment in medical textbooks.

THE CURRENT REGULATORY PARADIGM IMPEDES SCIENTIFIC DISCOURSE.

FDA prohibits any promotion by manufacturers related to off-label uses of a drug or device. The question then becomes: what is promotion? The current regulatory approach limits the ability of a manufacturer to share data not referenced in the package insert. This means that much valuable information may never be conveyed to clinicians and other medical decision-makers. Essentially, we do not get the benefit from data that has not been derived from randomized, controlled clinical trials.

Sharing comprehensive, scientifically valid data is critical to the practice of medicine generally, and it is even more critical for particular specialties. It is sometimes claimed that the use of drugs or devices off-label is the result of a choice by physicians. While sometimes this is true, for pediatric cardiologists and electrophysiologists, this is usually not the case. This is due to the fact that very few of the medications for arrhythmias that are on the market are formally approved for use in children. Thus, using treatments off-label is often our main method of treatment. Similarly, catheters that we use for catheter ablation procedures are labelled for a limited number of specific arrhythmias, but are used by all electrophysiologists (adult and pediatric) for treating and curing all types of arrhythmias.

By way of example, I will cite the example of amiodarone, brand name Cordarone. This is one of the most important medications for the treatment of potentially life-threatening arrhythmias, particularly in patients who have undergone successful surgical repair of complex congenital heart defects but who have dangerous arrhythmias in the aftermath of surgery. The

FDA-approved label simply states “The safety and effectiveness of Cordarone Tablets in pediatric patients have not been established.”

There are an additional six months of exclusivity granted to manufacturers of medications who generate data related to pediatric populations, under the Pediatric Research Equity Act (PREA) but this has not been sufficient to produce the amount of shareable data we might like, particularly for older drugs. As such, our clinical decisions often rest on anecdotal evidence and informal information-sharing among physicians. This is not an ideal environment in which to make treatment decisions.

Another example that I might cite, not specific to children, is labelling of ablation catheters. These devices are used in performing curative catheterization procedures, and these procedures have essentially replaced open heart surgery as the best option for a curative procedure for the last 25 years. Their labelling is limited to only certain arrhythmias. For example, the Cryocath Freexor-Xtra cryoablation catheter (manufactured by Medtronic) is only labelled for treating one arrhythmia, atrioventricular node reentry tachycardia (AVNRT) despite the fact that it is ideal for treating tachycardia due to accessory pathways located close to the normal conduction system without risking inadvertent atrioventricular block. It would be absurd to use a different catheter for this indication on the basis of the labelling, and even more absurd to consider open heart surgery. However, because of the labelling, technical support representatives of the manufacturer are not allowed to discuss this indication directly, despite the fact that the use of this catheter for this indication is widely agreed to be the standard of care.

There is an important way in which this information-sharing among physicians may also be adversely affected. When a medical conference is directly sponsored by a manufacturer, these conferences do not qualify as continuing medical education (CME) events based on rules of the

Accreditation Council on Continuing Medical Education (ACCME). Consequently, physician speakers are considered to be “agents” of the manufacturer sponsoring the event, and so they are also limited to discussing only the labelled indications. Any discussion between physicians regarding experiences with drugs or devices that are off-label at such events must occur informally, rather than as part of the program, and thus these discussions do not benefit from the great potential for information sharing among physician attendees. Such discussions can occur formally at medical and scientific conferences not directly sponsored by industry, but this rule limits the opportunities for such information sharing of data related to children.

The good news is that it doesn’t have to be this way. It is likely that there is a large amount of data maintained by manufacturers, which, under the current regulatory structure, manufacturers are not allowed to proactively share with clinicians. I recommend that the Committee develop ways to work with FDA to unlock this data. I also would like to respectfully suggest a few parameters to ensure this is done in a responsible manner.

REGULATION SHOULD DISTINGUISH BETWEEN PROMOTION AND DATA-SHARING.

There is a difference, in my view, between advertising an unapproved use to the public versus sharing scientifically valid data with clinicians, and this difference can be reflected in the regulatory approach to each type of activity. There is a vast space between our current regulatory approach and a “Wild West” approach. In my opinion, the appropriate and responsible regulatory approach likely lies somewhere in the middle.

I urge the Committee to explore ways to define acceptable real-world evidence that manufacturers can proactively share with medical decision-makers. These types of data may

include observational studies, pharmacoeconomic studies, or information on subpopulations. The data must be truthful, presented in context, and scientifically valid.

There is some concern that manufacturers might overwhelm physicians with data taken out of context, or data that is misleading and skewed to present a more favorable picture than is realistic. However, physicians are trained to analyze data. We know how to evaluate the validity of studies. If regulatory restrictions provide guardrails to ensure that the data is truthful and presented in context, physicians are fully capable of analyzing such data effectively.

As I noted previously, a reasonable regulatory paradigm lies somewhere between no communication and completely unrestricted communication. However, the current structure is not serving to foster the advancement of medical knowledge, and it leaves many patients and their physicians at an unnecessary disadvantage. Additionally, it seems incongruous that the manufacturer – the entity with the most robust data related to a product – cannot share the information they hold proactively, while any layperson with an internet connection can freely disseminate whatever information they like about that same product, however biased and unreliable.

CLOSING

I hope that my testimony has provided the Committee with a real-world perspective on how current FDA policy is preventing physicians from receiving valuable, clinical information in a timely fashion. In closing, I respectfully suggest that Congress should establish ways to unlock data maintained by manufacturers related to off-label conditions and populations. I thank the Committee for its time and look forward to working with you on policy proposals related to this topic.

Mr. BURGESS. The Chair thanks the gentleman for his testimony. Dr. Kesselheim, you are recognized for 5 minutes for your statement, please.

STATEMENT OF AARON S. KESSELHEIM

Dr. KESSELHEIM. Good morning, Chairman Burgess, Ranking Member Green, and other members of the committee, thank you for the opportunity to join you today. In my time I want to make four main points.

First, the current restrictions on manufacturers' ability to market their drugs for non-FDA-approved indications is not a bureaucratic or paternalistic effort to prevent manufacturers from communicating. These rules were developed in response to major public health problems caused by the lack of such regulation. Evidence of the public health dangers that arise from widespread off-label marketing can be seen in the drug paroxetine or Paxil, an antidepressant that was promoted off-label for use in children leading to at its peak over two million prescriptions per year for use in children until it was ultimately linked to self-injury and suicide in that population. Or, the off-label promotion of anti-psychotic medications to control behavioral symptoms in elderly patients with dementia, uses that are not only generally ineffective, but that also increase the risk of death by 60 to 70 percent.

At one point, due to off-label promotion approximately one in seven elderly nursing home residents reportedly received these drugs.

Over and over again, these episodes show us, as former Chief Justice William Rehnquist originally put it that "there are sufficient dangers attending [the] widespread use [of pharmaceuticals] that they simply may not be promoted in the same manner as hair creams, deodorants, and toothpaste."

Second, the dangers from off-label promotion do not come simply from the spread of false information about these products, although that does happen on occasion of course. Rather, in one study that I led, we found that off-label promotion most commonly involved presenting reports of individual cases or poorly designed studies as definitive evidence supporting an off-label use, while de-emphasizing data that didn't fit the narrative the manufacturers were creating. In each of these particular cases, the words themselves may not have been false or strictly misleading, but the benefits of the drug overstated and the risks down played in ways that the physicians might have needed advanced training in epidemiology or access to the underlying clinical trial data to understand which they simply do not have. This is why we need the diligent, independent assessment of safety and efficacy provided by the FDA. The complexity of the assessment that is required, along with the high stakes of getting that assessment wrong provides the rationale for having a formal drug approval process in the first place.

Third, the Griffith and Guthrie discussion drafts directly risk these outcomes. The Guthrie discussion draft, for example, defines scientific information that could support an off-label marketing claim as including preclinical data in petri dishes or in mice, and all it requires is a study that was conducted that the manufacturer anticipates could be sufficient to support FDA approval.

The Griffith draft, in creating a so-called safe harbor for scientific exchange, purports to require manufacturers to disclose appropriate contextual information for their statements, but it would be highly risky to give a manufacturer with a strong financial and intellectual stake in the product's success free reign to determine what is or isn't proper context or what is or isn't contradictory for its product. At the same time, it is unrealistic to expect each individual physician to have the time and expertise to subject such claims to the same kind of scrutiny that the FDA would exercise when it reviews a drug application or a request for a new indication.

The drafts also purport to protect the public health by attaching disclaimers to these off-label communications, but I led a systematic review of the evidence about the impact of such disclaimers, most of which currently come in the context of promotional statements for herbal remedies and dietary supplements for which Congress eliminated FDA oversight of promotion more than 20 years ago. Many of these products advertise health-enhancing effects despite no legitimate evidence that they work with disclaimers that the FDA has not evaluated the promotional claims, but the massive collective evidence reveals that such disclaimers fail to adequately inform or modify consumer behavior. So when anybody proposes a disclaimer, I suggest that there be a disclaimer, that disclaimers don't actually work.

Finally, I want to emphasize that the current system helps protect patients from widespread promotion of drugs and devices for potentially unsafe and ineffective off-label uses, while still permitting off-label prescribing at the discretion of physician and patients and providing well-circumscribed avenues for manufacturer communication about these issues such as in response to bona fide questions arising from physicians. By contrast, the Griffith and Guthrie discussion drafts would reduce manufacturers' incentives to conduct well-controlled trials of potential off-label uses in the first place. Instead, as Representative Green mentioned, manufacturers would be incentivized to seek approval of drugs and devices for the narrowest indication possible, and then conduct "studies" of variable quality showing the utility of these products for unapproved indications that would not meet current FDA standards for scientific rigor.

I strongly recommend that the committee not pursue these drafts and instead consider how we can give the FDA the proper resources and authorities to continue to review emerging data efficiently so that evidence that does support new uses of drugs and devices can be incorporated into their labels and clinical practice while uses that the totality of the data show are unsafe can be identified for the benefits of patients. Thank you very much.

[The prepared statement of Dr. Kesselheim follows:]



PORTAL
Program on Regulation, Therapeutics, And Law



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**The Public Health Risks of Expanding Off-Label Promotion
of Prescription Drugs and Devices**

Aaron S. Kesselheim, M.D., J.D., M.P.H.

Associate Professor of Medicine, Harvard Medical School and Brigham and Women's Hospital

Subcommittee on Health
Committee on Energy and Commerce
U.S. House of Representatives
July 12, 2017
Washington, D.C.

Summary

- The Guthrie and Griffith discussion drafts dangerously expand the permitted range of off-label statements for manufacturers. Current rules restricting off-label promotion exist because of major public health problems that have arisen from lack of regulation of manufacturer promotional activities.
- Expanding the range of off-label communications will expose patients to drugs that may not work or for which the safety has not been adequately established, and potentially divert use from drugs that we know have benefits that outweigh their risks because they have passed FDA review. It will also increase health care costs by increasing use of inadequately tested, costly products.
- The FDA's independent assessment of the benefits and risks of drugs and high-risk devices can help ensure that information is not communicated to physicians or patients that gives an incorrect impression of the utility of the product at issue (even if it isn't clearly "false")
- The Guthrie and Griffith discussion drafts suggest that disclaimers could help protect patients, but available evidence indicates that disclaimers on health-related promotional statements fail to adequately inform or modify consumer behavior
- Expanding off-label promotion would reduce manufacturers' incentives to conduct well-controlled trials of potential off-label uses in the first place, incentivizing manufacturers to seek approval of drugs and devices for the narrowest indication possible and then conduct "studies" of variable quality showing the utility of these products for unapproved indications that would not meet the current FDA standards for scientific rigor.

Chairman Burgess, Vice-Chairman Guthrie, Ranking Member Green, and other members of the committee:

My name is Aaron Kesselheim. I am an internal medicine physician, lawyer, and health policy researcher in the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital in Boston and an Associate Professor of Medicine at Harvard Medical School. I lead the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research core that studies the intersections between laws and regulations and the development, utilization, and affordability of drugs. We are the largest, academic-based independent group conducting empirical research in this area in the country. Thank you for this opportunity to provide my views on the communication and marketing of medical products for off-label uses and the discussion draft documents from Reps. Griffith and Guthrie.

The current restrictions on manufacturers' ability to market their drugs for non-FDA-approved indications are not a bureaucratic or paternalistic effort to restrict manufacturers from communicating to physicians about their products. Rather, these rules were developed over the last century in response to major public health problems caused by the lack of regulation of manufacturer promotional activities. The notion that the FDA must validate a drug's or device's efficacy and safety was a response to public health tragedies in which patients died after taking products with poisonous constituents (sulfanilamide elixir, 1938), gave birth to babies with devastating congenital anomalies (thalidomide, 1962), or used contraceptive devices that caused bacterial sepsis (Dalkon Shield, 1974), all of which occurred in the context of wide manufacturer promotion of the safety of these products.¹ Even more common was the promotion of drugs to

¹ Kesselheim AS and Mello MM. Prospects for regulation of off-label drug promotion in an era of expanding commercial speech protection. *Univ North Carolina Law Review* 2014;92:1539-1604.

treat conditions for which they totally lacked efficacy. From these episodes, we learned, as former Chief Justice William Rehnquist put it, that “there are sufficient dangers attending [the] widespread use [of pharmaceuticals] that they simply may not be promoted in the same manner as hair creams, deodorants, and toothpaste.”² Rather, it was in the public’s interest for an independent body of experts—the FDA—to validate that a medication or high-risk device actually worked before it could be sold and promoted for a particular use.

Despite these rules, the past two decades has revealed that off-label promotion is quite common in the drug and medical device industries. Nearly every major drug manufacturer has now been investigated by government prosecutors for its off-label promotional practices. All of these cases also involved important risks to public health related to the off-label uses. A partial list of products for which inappropriate off-label marketing has led to patient morbidity and mortality includes:

- Rofecoxib (Vioxx), an anti-inflammatory drug linked to anywhere from 30,000 to over 130,000 heart attacks and sudden cardiac deaths because of inappropriate promotion.³
- Paroxetine (Paxil), an antidepressant promoted off-label for use in children, leading to 2 million prescriptions in children and adolescents in the year 2002 alone,⁴ that was linked to self-injury and suicide.⁵
- Numerous antipsychotic medications were prescribed to control behavioral symptoms in elderly patients with dementia, uses that were not only generally

² Virginia State Bd. of Pharmacy v. Citizens Consumer Council, 425 U.S. 748 (1976).

³ <https://www.finance.senate.gov/imo/media/doc/111804dgttest.pdf>

⁴ <http://www.bmj.com/content/351/bmj.h4629>

⁵ <http://www.bmj.com/content/351/bmj.h4320>

ineffective but that also increases the risk of death by 60 to 70%. Its promotion led to about one in 7 elderly nursing home residents receiving these drugs.⁶

Settlements of government investigations of these off-label marketing episodes have led to over \$15 billion in civil and criminal fines.

In these cases, the manufacturers were not necessarily going around spreading falsehoods about their products to get physicians to prescribe them. (That did happen on occasion, of course.) Rather, manufacturers and their promotional salespeople might present anecdotal evidence of benefits from uncontrolled case series. Or they might show doctors the results of observational studies that actually had important design flaws not recognizable unless someone had advanced training in pharmacoepidemiology. Or they might describe the results of clinical trials strategically designed to show favorable outcomes. In one study of off-label marketing practices that I led, we found that 75% of the cases involved self-serving presentations of the literature through which physicians were given unbalanced study data supporting the unapproved use.⁷ A common example was selective presentation of favorable studies, where dangers from the off-label uses allegedly being promoted were not mentioned. Other examples included presenting one drug as being superior to another when no head-to-head studies had been conducted and characterizing reports of individual cases or poorly designed studies as definitive evidence supporting an off-label use. In each of these particular cases, the words themselves may not have been false or strictly misleading, but physicians were given an incomplete picture of the use of the drug, leading to off-label prescribing and substantial patient harms. This is why we need the diligent, independent assessment of whether a drug or high-risk device is safe and effective for an intended use that is provided by the FDA, which

⁶ US Office of Inspector General. Medicare Atypical Antipsychotic Drug Claims for Elderly Nursing Home Residents. May 4 2011. Available from: <https://oig.hhs.gov/oei/reports/oei-07-08-00150.asp>

⁷ Kesselheim AS, Mello MM, Studdert DM. Strategies and practices in off-label marketing of pharmaceuticals: a retrospective analysis of whistleblower complaints. *PLoS Medicine* 2011;8(4):e1000431.

can involve dozens of scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials.

However, the Griffith and Guthrie discussion drafts dangerously expand the permitted range of off-label statements for manufacturers. The Guthrie discussion draft defines “scientific information” that could support an off-label marketing claim as including “pre-clinical” data and all it requires is that a study was conducted that a manufacturer “anticipates could be sufficient” to support FDA approval and that the manufacturer “intend” that a supplemental application will be submitted at some undetermined time in the future. The Griffith draft, in creating a so-called “safe harbor” for scientific exchange, purports to require manufacturers to disclose the “appropriate contextual information” for their statements. But it would be highly risky to give a manufacturer with a strong financial and intellectual stake in the product’s success free rein to determine what is or isn’t proper context, or what is or isn’t contradictory, for its product. At the same time, it is unrealistic to expect each physician to have the time and expertise to subject such claims to the same kind of scrutiny that the FDA would exercise when it reviews a drug application or a request for a new indication. In these situations, we need the FDA to act as a learned intermediary on behalf of prescribing physicians, who can then synthesize the available data and make judgments about risks and benefits for their patients.⁸ The complexity of the assessment that is required, along with the high stakes of getting the assessment wrong, provides the rationale for having a formal drug-approval process in the first place.

The Griffith and Guthrie drafts also purport to protect the public health by attaching disclaimers to their vast expansions of manufacturers’ abilities to engage in off-label communication. I led a systematic review of the evidence about the impact of disclaimer related to health-related claims

⁸ Kesselheim AS and Avorn J. Pharmaceutical promotion to physicians and First Amendment rights. *New England Journal of Medicine* 2008;358:1727-1732.

of medical products.⁹ Most such data has been gathered in the context of promotional statements for herbal remedies and dietary supplements, for which Congress eliminated FDA oversight of promotion more than 20 years ago in the Dietary Supplement Health and Education Act of 1994. The result has been the proliferation of untested, ineffective, and frequently unsafe products that fill store shelves and patients' medicine cabinets and consume about \$32 billion of health care resources in the US, often with no demonstrable benefit. Many of these products advertise health-enhancing effects and bear disclaimers that the FDA has not evaluated the promotional claims, but the mass of collected evidence reveals that such disclaimers generally fail to adequately inform or modify consumer behavior. There is no scientific basis for believing that disclaimers would function any better in this context.

Expanding permitted off-label communications will expose patients to drugs that may not work or for which the safety has not been adequately established. It will also potentially divert use from drugs that we know have benefits that outweigh their risks because they have passed the usual FDA requirements. The result will also be increased health care costs, due to broader use of inadequately tested, costly products. Such effects are predictable because decades of evidence show that manufacturer promotion is a powerful force in shaping and directing physician prescribing and influencing physician knowledge in ways that favor the product being promoted, as opposed to the evidence-based practice. By contrast, the current system helps protect patients from widespread promotion of drugs and devices for potentially unsafe or ineffective off-label uses, while still permitting off-label prescribing at the discretion of physician and patients and providing well-

⁹ Kesselheim AS, Connolly JC, Rogers J, Avorn J. Despite mandatory disclaimers on dietary supplements, many consumers remain unaware or overlook the information. *Health Affairs* 2015;34(3):438-446.

circumscribed avenues for manufacturer communication about these uses, such as in response to bona fide questions arising from physicians.

Finally, the Griffith and Guthrie discussion drafts, if enacted into law, would reduce manufacturers' incentives to conduct well-controlled trials of potential off-label uses in the first place. Instead, manufacturers would be incentivized to seek approval of drugs and devices for the narrowest indication possible, and then conduct "studies" of variable quality showing the utility of these products for unapproved indications that would not meet the current FDA standards for scientific rigor.¹⁰ Many studies would predictably appear to support claims of efficacy, and those that best met marketing aims could be selected for emphasis in promotional campaigns, with the others relegated to footnotes or ignored. I strongly recommend that the committee not pursue these drafts and instead consider how we can give FDA the proper resources and authorities to continue to review emerging data efficiently so that evidence that does support new uses of drugs and devices can be incorporated into their labels and clinical practice, while uses that the totality of data show are unsafe can be identified for the benefit of patients.

¹⁰ Kesselheim AS, Mello MM, Avorn J. FDA regulation of off-label drug promotion under attack. *JAMA* 2013;309(5):445-446.

Mr. BURGESS. The Chair thanks the gentleman.

Ms. House, you are recognized for 5 minutes for an opening statement, please.

STATEMENT OF LINDA HOUSE

Ms. HOUSE. Good morning. My name is Linda House, and I am the president of the Cancer Support Community. I would like to thank the committee for allowing us to be here and share this testimony today.

The Cancer Support Community is an international nonprofit organization whose mission is to ensure that all people impacted by cancer are empowered by knowledge, strengthened by action, and sustained by community. Our organization sees over 100,000 patients and families each year through a network of affiliates around the world. We also have a Cancer Support Helpline where we administer through both of those properties, over \$50 million of evidenced-based care and support each year free of charge to patients and their families. Importantly, CSC is also home to the only Research and Training Institute of its kind whose mission is to collect and analyze information from patients to elevate the voice of the patient and the caregiver as it relates to their cancer experience.

I am here today to bring you what I feel is the most important voice to this conversation and that is the voice of the patient.

The last 20 years have delivered unprecedented growth in innovation across all aspects of health care. Never before has a patient had so many options for diagnosis, treatment, and follow-up care as they do now. Patients are more educated. They are more engaged. They are more empowered consumers of health care than ever before. Yet, despite the emergence of patients as important players, and even leaders of their care teams, accessibility to comprehensive information continues to be elusive.

We will be releasing data next week from our Cancer Experience Registry where we have learned that 50 percent of patients engage in shared treatment decision making with their healthcare professionals. Only about eight percent report allowing healthcare professionals to make decisions without their input. Yet, only 25 percent indicate that they feel like they are prepared to have those treatment decisions.

Importantly, our data reflects a growing concern about inadequate collection, reporting, and label updating of endpoints that are meaningful to patients. In our research, 93 percent of respondents considered quality of life as very important when making treatment decisions. Quality of life measured higher than length of life, and these are people with cancer, yet product labels continue to focus very little on fully measuring comprehensive quality of life metrics. Further, product labels almost never reflect updates when there are findings beyond the clinical trial setting including findings about long-term effects which would be meaningful for patients. A system that does not proactively collect, publish, and share data poses a significant risk to patient care.

There are a few issues I would like to raise as current limitations and we do support the work that the FDA does and we do support

the work of the clinical trial systems and we do support accurate, meaningful, nonpromotional communication.

Preapproval information, as you know, is when clinical data is available on a product prior to the product having an FDA label. According to PhRMA, it takes an average of 10 to 15 years for a drug to make it to market. And during that time, much is learned about the way in which the drug works in the body, how the body works with the drug, what is the accurate dose, what is the toxic dose, and what are the side effects associated with that drug. Yet, this treasure trove of information remains out of reach from individuals other than the sponsor or potential trial investigators.

Number two, limiting communication of information to only that which is reflected in the label poses a significant challenge to patients. CSC appreciates the work of the FDA and sponsors of phase IV studies, in particular, but recognizes that these studies do not capture comprehensive data for the use of the product as was mentioned in the real world. Also, it is a rare occurrence for the label to be updated in a manner that would allow for proactive communications of findings outside of the controlled clinical trial setting. And as we know, once trials go into broader, less controlled situations, they perform differently in those patients.

Number three, data accumulated through Investigator Initiated Trials on diseases that would never reach the investment potential for registration in a label is extremely important to clinical care. This information may never be communicated to clinicians and will almost certainly not be made available to patients who may benefit from the findings and this is particularly important in patients with rare disease.

Number four, information learned outside of the clinical trial setting and not captured in the label can also have a true impact on the patient experience. And as I submitted in my written testimony, this could be things like burning at the injection site, a reduction in fatigue by understanding how to better supplement the treatment. That information is not in the label and cannot be shared in a proactive way.

Number five, there are several elements in general clinical practice that are continuing to contribute to the limitation that patients have to access comprehensive medical information through their healthcare team. And in particular, as there is an active evolution of the care delivery systems from volume to value, it has brought with it efficiency and cost containment strategies that focus on limiting treatment decisions. And I am talking about hospital-based formularies and clinical pathways that are currently being used in physician practices.

Number six, there is an inconsistent practice and reinforcement of publishing clinical trial data results in scientific journals and other databases. This information has to be published and as mentioned in my written comments, the ratio of trials that have been opened, closed, and published, the compliance rate with that abysmal and there must not only be requirements, but also enforcement of the requirements to ensure that all results of trials be posted whether those results are positive or negative.

Finally, industry interpretation of the current regulations is applied inconsistently across companies. This impacts the way in

which industry communicates with all stakeholders and most certainly the way in which industry communicates with patients and families forcing them only through the direct-to-consumer marketing channel.

So in conclusion, while the comments that I have made have simply scratched the surface on what is a much broader and deeper issue, it is my hope that I have highlighted in your mind the perspective of patients who are living with chronic and life-threatening illness across the United States.

And to summarize in specific areas where we would like to continue to work with the committee and the FDA, patients and healthcare providers must have access to medical research findings in a comprehensive and real-time manner. Product labels should be updated in a timely manner and include data from endpoints that matter most to patients and/or there must be another mechanism by which to capture and proactively communicate findings that are clinically meaningful and relevant. Scientifically sound communications about safe and effective uses of a product are essential and should be made available to all stakeholders. Clinical trial results, positive and negative, should be published by the trial sponsor in a period of time that is reasonable to allow full and meaningful data review while ensuring timely access to information. Data, positive and negative, collected outside of the clinical trial process, inclusive of real-world evidence that is collected and analyzed with appropriate scientific rigor should be published and made available to stakeholders. And finally, proactive medical communication should be tailored to meet the needs and literacy levels of specific stakeholders and should not, for any stakeholder, be limited only to the product label which may not yet exist or be outdated.

Thank you for allowing us to be here.

[The prepared statement of Ms. House follows:]



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**United States House of Representatives The Energy and Commerce Committee
Hearing: Examining Medical Product Manufacturer Communications
July 12, 2017**

**Written Remarks Submitted by: Linda House, MSM, BSN, RN,
President, Cancer Support Community**

Good morning, my name is Linda House, and I am the President of the Cancer Support Community (CSC) global headquarters. Thank you to Chairman Walden, Vice Chairman Barton, Ranking Member Pallone, and all of the members of the Energy and Commerce Committee for allowing me to join you today and offer this testimony.

The Cancer Support Community is an international nonprofit organization whose mission is to ensure that all people impacted by cancer are empowered by knowledge, strengthened by action and sustained by community. CSC serves over 100,000 patients and families annually through a network of 150 affiliate sites and satellite locations across the country as well as through the *Cancer Support Helpline* where patients and their families receive evidence-based programming and social and emotional support. The CSC network delivers close to \$50 million in services, free of charge, each year. CSC is also home to the only *Research and Training Institute* focused on collecting and analyzing data to understand and elevate the patient and caregiver voices about the cancer experience.

Thank you for the opportunity to speak with you this morning regarding medical product manufacturer communication.

The Patient Perspective

I am here today to bring you the most important voice in this discussion regarding medical product manufacturer communication—that of the patient. As you may have seen, CSC joined seven other national organizations to submit a response to the Food and Drug Administration's (FDA) recent guidance on this very important issue. We appreciate the FDA's efforts to provide additional guidance in this area and look forward to working with the Agency in the coming months and years to ensure its regulations reflect the best interests of patients.

The last twenty years have delivered unprecedented growth in innovation across all aspects of health care. Never before has the patient had so many options for diagnosis, treatment, and follow-up care. Patients are more engaged, educated, and empowered consumers of their health care than ever before. Yet, despite the emergence of patients as important players—and even leaders—of their care teams, accessibility to comprehensive information continues to be elusive.

The Cancer Support Community will release new survey data next week that outlines the patient experience with treatment decision-making among other factors associated with the cancer



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experience. In our research, we learned that nearly half of all the patients we surveyed made treatment decisions together with their care teams while only 8% leave their treatment decisions fully to their care team. Yet, the data also underscores that patients feel unprepared to make these choices with 1 in 4 reporting that they did not at all feel prepared to discuss treatment options with their physicians.

The data also reflects a growing concern about inadequate collection, reporting, and label updating of endpoints that are meaningful to patients. In our research, 93% of respondents considered quality of life as “very important” when weighing treatment options. Quality of life measured higher than length of life (79%), yet product labels continue to focus very little on fully measuring comprehensive quality of life metrics. Further, product labels almost never reflect updates when there are findings beyond the clinical trial setting including findings about long-term effects that would be meaningful to patients (e.g., neuropathy with chemotherapy administration). A system that does not proactively collect, publish, and share data poses a significant risk to patient care.

Current Limitations

As a starting point, I would like to ground us in a set of long-standing institutional as well as regulatory limitations that restrict the flow of information to patients.

At the core of the FDA’s mission is the responsibility to protect the public health. We wholeheartedly support the FDA in this core mission and are eager to work with the agency to meaningfully meet this goal. However, current regulatory requirements create barriers for patients to secure a full complement of relevant and meaningful information on treatment options for their conditions.

“Pre-approval” information is when clinical data is available on a product prior to the product having an FDA label. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), it currently takes an average of 10 to 15 years to bring a drug to market. During that time, much is learned about the way in which the drug works in the body, how the body responds to the drug, the accurate dose, the toxic dose, and the associated side effects. Yet, this treasure trove of information remains out of reach from individuals other than the sponsor and trial investigators. The proactive sharing of information learned during the development stage is subject to pre-approval promotion regulations of the FDA. This is problematic for many of the patients who are being asked to participate in the clinical development process of the 7,000 drugs in clinical development today. A patient’s ability to learn about earlier phase information regarding safety or efficacy signals is severely limited. For example, just last week, I was approached on behalf of a patient who was asked to go on a phase II trial for a new drug for a certain type of lung cancer (alk +). Having my own questions about safety and efficacy in the earlier phases of development, including the therapeutic dose, why phase II instead of the phase III trial, I spent time searching publicly available documents. After spending well over 90



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minutes searching, I, an educated consumer, could find only 2 pieces of information that referenced safety and efficacy. The reality is that the early phase results are very promising and relevant to this patient, but they were not proactively shared with him at the time of the request to join the trial and finding them were not intuitive. I would also add that only one of the 2 pieces of information I found was published in a peer-reviewed forum.

Limiting communication of information to only that which is included in the product label poses significant challenges to patients. Product labels reflect information collected in the controlled clinical trials setting with specified patient populations. It is widely observed that the performance of a drug may be different once it is introduced into general use, which will likely be a broader, less-controlled population. CSC appreciates the work of the FDA and sponsors of phase IV studies, but also recognizes that these studies do not capture comprehensive data for the use of a product in the real world. Also, it is a rare occurrence for the label to be updated in a manner that would allow for proactive communication about findings.

Additionally, data may be accumulated through Investigator Initiated Trials (IITs) on diseases that would never reach the investment potential for registration and a label, yet the data may be extremely relevant for clinical care, both positive and negative. This information may never be communicated to clinicians and will almost certainly not be made available to patients who may benefit from the findings. One example of this is lupus treatments. According to the Lupus Foundation of America, there are 1.5 million Americans living with the disease. Yet according to the FDA's website, there are only 4 drugs approved to treat lupus—Aspirin in 1948 followed by corticosteroids (year not listed), a drug originally used as an anti-malarial (Plaquenil) in 1955 and, most recently, Benlysta in 2011. The reality for patients with lupus is that there are many treatments being used to treat their disease in an off-label manner. The lack of proactive communication on the safe and effective use of these “off-label” indications is arguably a patient safety and well-being issue. This example only begins to illustrate the challenges for any patient facing a rare condition.

Information learned outside of the clinical trial setting and not captured in the label can also have a true impact on the patient experience. I saw this a number of times in my role as a medical information administrator for a large pharmaceutical company. In that role, I was charged with answering unsolicited medical questions about a product approved for certain cancers. There are two situations that I will always carry with me to illustrate this. First, I received several reports each week from the sales representatives stating that their customers were repeatedly saying that patients were complaining about burning at the injection site when the intravenous medication was started. Upon investigating the potential issue, I found that when reconstituted, the pH of the product was acidic (around 2.7 to 3.3) which caused burning when coming in contact with the vein wall. A simple solution to this was to place a warm compress at the injection site prior to turning on the infusion. Yet, because this solution was not a part of the product label, it could not be proactively shared with patients or clinicians. The second example dealt with fatigue



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experienced by patients in the immediate 24 to 48 hours post administration. There was a small, published study that demonstrated the administration of low-dose steroid at 8, 16, and 24 hours post administration significantly reduced the patient experience with fatigue. Again, this was not a part of the label and could never be shared proactively with patients and clinicians. Both had a significant impact on patient quality of life.

There are several elements in general clinical practice that contribute to the limitations of patients having access to comprehensive information through their health care team. CSC acknowledges that these may be collateral effects versus the withholding of information, but the outcomes for patients are real nonetheless. The active evolution of the care delivery system from volume to value has brought with it efficiency and cost-containment strategies that focus treatment decisions on a limited selection. One example is institution or system level formularies where hospitals or large systems (e.g., the Veterans Administration) have a limited list of treatment options available for their health care providers to consider as they make treatment decisions for their patients. A second example is the implementation of clinical pathways which are based on scientific information but essentially limit treatment options for patient use. Even more concerning is that a clinical pathway used in one practice may be different than the pathway for the same disease used in another practice. The lack of transparency regarding the data used to make formulary and pathway decisions coupled with the limited patient access to comprehensive information sets is simply unacceptable as we move towards patient centricity as the gold standard.

Another limitation is the inconsistent practice and reinforcement of publishing clinical trial results in scientific journals and other databases (e.g., clinical trials.gov). Findings secured through the clinical trial process, whether positive or negative, may never become a part of a product label, but certainly offer meaningful contributions to the overall body of scientific knowledge. A study by Riveros and colleagues (2013) analyzed 600 trials with results posted on clinicaltrials.gov. They found that 50% of the trials did not have a corresponding published article. Even more alarming are the results found by Anderson and colleagues (2015) which looked at 13,327 trials that had terminated or completed between January 1, 2008 and August 31, 2012. Of the trials, 13.4% posted summary results within 12 months after trial completion, and only 38.3% reported results as of September 27, 2013. The findings from these trials offer meaningful information for patients and providers in both clinical practice and also as foundational knowledge for further drug development and clinical trial participation. There must not only be requirements but also enforcement of requirements to ensure that all results of all trials be posted and/or published within a reasonable period of time.

Finally, industry interpretation of the current regulations are applied inconsistently across companies. This may impact the way in which industry communicates with all stakeholders, but it almost universally results in industry choosing not to speak with the patient or family with the exception of direct-to-consumer advertising tactics. Guidance should be issued and enforced to



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allow patients and families to, at a minimum, secure answers to questions they may have about products they are taking. One very recent example was a call that I made to the medical information line of a pharmaceutical company to inquire about transferring a topical anesthetic from a very large and non-travel compliant tube to a smaller, travel compliant container. The question was whether the transfer from the original container would impact the integrity of the product. The response from the pharmaceutical company was that I would have to speak with my physician to secure the answer.

Recommendations

While these comments have simply scratched the surface on a much broader and deeper issue, it is my hope that I have highlighted in your mind the perspective of patients living with chronic and life-threatening illnesses across the United States. To summarize, the specific areas where we would like to partner and continue to advance the work of this committee, the FDA, and trial sponsors include:

1. Patients and health care providers must have access to medical research findings in a comprehensive and real-time manner.
2. Product labels should be updated in a timely manner and include data from endpoints that matter most to patients and/or there must be another mechanism by which to capture and proactively communicate findings that are clinically meaningful and relevant.
3. Scientifically sound communications about safe and effective uses of a product are essential and should be made available to all stakeholders.
4. Clinical trial data results, positive and negative, should be published by the trial sponsor in a period of time that is reasonable to allow full and meaningful data review while ensuring timely access to information.
5. Data, positive and negative, collected outside of the clinical trial process, inclusive of real-world evidence that is collected and analyzed with appropriate scientific rigor should be published and made available to stakeholders.
6. Proactive medical communication should be tailored to meet the needs and literacy levels of specific stakeholders and should not, for any stakeholder, be limited to only the product label which may not yet exist or be outdated. This includes physicians who are generalists and also specialists, allied health care providers (e.g., nurses and pharmacists), payers, and patients.

Thank you again for the opportunity to bring the patient voice to this important discussion. The Cancer Support Community along with many of our partners in the patient advocacy community stand ready to help improve patient and provider access to information that is vital to planning care for and improving outcomes for patients.



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Mr. BURGESS. Thank you. Thank you for your testimony.
 Ms. Khachatourian, you are recognized for 5 minutes, please.

STATEMENT OF KATHERINE WOLF KHACHATOURIAN

Ms. KHACHATOURIAN. Thank you to Chairman Burgess, Ranking Member Green, and members of the Subcommittee on Health for providing me the opportunity to speak before you today.

I am Katherine Khachatourian, a pharmacist working in Medicare health insurance and a member of the AMCP Professional Practice Committee.

Imagine a world where you are required by Federal and State laws to determine a budget and coverage criteria for all drugs 8 to 12 months in advance of the coverage year using limited available information while knowing there is information that could help you make more accurate and informed decisions. You just don't have the key to unlock the consistent release of that information. This is the world we live in as payers and population health decision makers.

The limitations on information we are able to obtain results in a hindrance to patient access to novel and emerging therapies, limits our ability to accurately forecast, plan, and budget for anticipated expenditures, and it precludes our ability to contract on value rather than volume. This is the reason I am here before you today, to demonstrate the need for a legislative framework in support of House Bill 2026 which will provide the key to unlock additional information needed for us to make informed benefit decisions for better patient access to treatment. These concepts have been discussed in depth with a diverse group of stakeholders including payers, manufacturers, clinicians, and patient advocacy groups who provide consensus recommendations for how, who, and what information should be exchanged prior to FDA approval. This information should be limited to a narrow audience inclusive of payers and population health decision makers. This scope does not include manufacturer communications with patients or prescribers prior to FDA approval.

Let me share a few personal examples where lack of information has decreased patients' timely access to treatment. In December of 2013 and October of 2014, the FDA-approved breakthrough treatments for the treatment of hepatitis C. These drugs had novel mechanisms of action which changed the landscape for patients with this diagnosis. Note, these approval dates were several months after we had already—one of the payers had already analyzed costs and planned benefit. Had we been able to discuss in advance of the approval of these treatments, we would have had a better understanding of the landscape, timing of approval of multiple products, the relevant patients for each treatment, and any clinical information that would help us to make better decisions and ultimately been able to treat more patients in a more effective manner without the subsequent criteria revisions that proceeded after the approval of these products.

More importantly, the lack of needed information can impede patient access as seen in the new treatments for Duchenne's Muscular Dystrophy. In this instance, the level of evidence required to deem products safe and effective met the requirements for FDA ap-

proval. However, due to the inability of payers and manufacturers to openly discuss the level of evidence required for coverage, payers are not covering these therapies at this time. This is why the bi-directional information exchange is important to understand the level of evidence available and necessary for coverage. This example has left patients in a situation where they cannot access therapy. Had payers been able to convey the level of evidence required for coverage, could we have avoided this situation? Perhaps.

Another patient access issue was one I experienced in the past year for a request for oncology. On September 21, 2016, we received a coverage request for a treatment of a patient diagnosed with inoperable lip cancer that had recently spread to their tongue. The FDA granted accelerated approval to expand the indications of an existing chemotherapy treatment on August 5, 2016 to include head and neck cancer. However, when we received the request for coverage, the labeled indications and data supporting the expanded indication were not publicly available. In this situation, had I had the ability to discuss the data in advance with the manufacturer, I could have been better prepared to discuss the requested treatment with the provider, rather than scrambling through clinicaltrials.gov and requesting a copy of the clinical trial from the manufacturer while the insured patient awaited my coverage decision.

Because we can only estimate when therapies will be approved, if we receive a coverage request shortly after FDA approval, the landscape still remains one of chaos and special requests to manufacturers until the data is published, compendia and guidelines are updated, and coverage criteria reflect these new and novel treatments.

I have demonstrated in the previous examples each of these breakthrough therapies represent innovations and the potential to change a patient's life, if they are able to gain access to treatment. The barrier to access to novel therapies is a population health decision maker's ability to have sufficient data and sophisticated discussions with those most informed about the utility of the products in a timely enough fashion to budget, plan and forecast it for the therapies coming to market.

In conclusion, this is an issue of great importance for patient access to emerging therapies where a diverse group of stakeholders have come together to develop consensus recommendations. This includes a very narrow audience and scope of exchange between manufacturers and payers only. We need your legislative support to better care for our patients. Thank you.

[The prepared statement of Ms. Khachatourian follows:]

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Written Statement for the Record

Energy & Commerce Committee, Subcommittee on Health

“Examining Medical Product Manufacturer Communications”

July 12, 2017

Katherine (“Kat”) Wolf Khachatourian, PharmD, MBA

Vice President of Pharmacy Services, Strategy, and Delegation Oversight

Qualchoice Health Plan Services, Inc.

&

Member of the Professional Practice Committee

Academy of Managed Care Pharmacy (AMCP)

Summary of Statement

Existing laws and regulations hinder the ability of biopharmaceutical manufacturers to share information proactively on emerging therapies with population health decision makers, who have indicated that waiting until FDA approval is often too late for the critical planning, budgeting, and forecasting associated with health benefit design, especially given the recent influx of high-cost medications and focus on value-based payment models, and that they need access to information about emerging therapies at least 12-18 months prior to FDA approval. Therefore, in September 2016, a diverse group of stakeholders came together to develop consensus recommendations on how to enable preapproval communications, while still maintaining appropriate safeguards to prevent this information from reaching unintended entities.

In January 2017, the FDA released a draft guidance document explaining how “FDA does not intend to object” to certain types of information being shared prior to approval. However, the draft guidance remains non-binding and does not provide the level of certainty needed to truly operationalize Pharmaceutical Information Exchange (PIE). Therefore, there is a need for Congress to engage in this topic to create a legislative safe harbor for PIE so that it is clear that the proactive dissemination of certain information does not violate the prohibitions against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. *H.R. 2026 – The Pharmaceutical Information Exchange (PIE) Act of 2017* incorporates the consensus recommendations developed by the multi-stakeholder group, creates a very narrow safe harbor for a very specific purpose, and will improve patient access to emerging medication therapies.

Statement

As the U.S. health care system evolves from a historical payment system based upon quantity and process to a modernized system rewarding quality and improved patient outcomes, the need for timely communication between biopharmaceutical manufacturers and population health decision makers (e.g. payors, provider sponsored health plans, pharmacy benefit managers, accountable care organizations, and integrated delivery networks) about emerging therapies is critical for the successful shift to a value-driven system. The current pipeline of therapies awaiting Food and Drug Administration (FDA) approval offer promising, but often costly, treatments or cures for chronic diseases that previously had few options for long-term management. However, existing laws and regulations hinder the ability of biopharmaceutical manufacturers to share information proactively on emerging therapies with population health decision makers. Allowing for proactive Pharmaceutical Information Exchange (PIE) on these pipeline therapies will help population health decision makers to identify cost offsets for other medical interventions that impact patient costs.

Three Main Imperatives Driving the Need for Communications Prior to FDA Approval

A. Planning, Budgeting, and Forecasting for Benefit Design - As a result of federal laws and state mandates, population health decision makers are required to evaluate their plan designs, formularies, and rates 12-18 months in advance to meet submission deadlines 6-9 months before the beginning of the intended plan year. For example, for the 2016 coverage year, population health decision makers analyzed 2014 data to submit their 2016 rates by spring 2015. The budget impact of new therapies that were approved by the FDA after spring 2015 could not be integrated into the 2016 rates.

As detailed in Appendix I, a recent prime example of the need for population health decision makers to account for new medications entering the marketplace was the introduction of novel treatments for hepatitis C infection in 2013. Population health decision makers were not properly prepared for the impact of these new therapies and the inaccuracies in budgeting and forecasting resulted in limited patient access to these medications. Had PIE been available during this timeframe, population health decision makers would have had better knowledge of the impact of the new hepatitis C medications, would have been able to better plan, budget, and forecast, and would have been able to minimize disruptions to patient access to these medications.

Therefore, accurate forecasting and rate setting is critical to ensure patients have continued access to affordable coverage for their health care needs. With rates being filed over a year in advance, proper planning, budgeting, and forecasting are integral for population health decision makers to accurately account for the impact of new therapies that will enter the market.

- B. **Value-Based Payment Models** - There is an increased focus on value-based payment models as evidenced by the Medicare Shared Savings Program and a range of initiatives launched and proposed by the Center for Medicare and Medicaid Innovation (CMMI). Successful implementation of value-based payment models requires understanding the overall value of a therapy, including how pharmacy spending can offset medical costs and vice versa. In addition, it requires downstream planning for population health decision makers to change plan design, formularies, and necessary contracts in advance of submitting rates at least a year in advance of the intended coverage year. Therefore, to increase the utilization of value-based payment models, it is important for

biopharmaceutical manufacturers and population health decision makers to be able to share information prior to FDA approval about emerging therapies to provide sufficient time to implement these models in a timely and effective manner upon FDA approval.

C. **Patient Access to Breakthrough Therapies** - *The Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)* created an expedited approval pathway allowing the FDA to grant priority review if preliminary clinical trials indicate a therapy may offer substantial treatment advantages over existing options for patients with serious or life-threatening diseases. Under the expedited approval pathway, therapies may be approved by the FDA before clinical trial data is published and made publicly available, thereby making it very difficult for population health decision makers to determine whether a therapy is appropriate for a patient if they receive a coverage request prior to publication of the data. Guidelines and peer-reviewed compendia sources are even further delayed in providing population health decision makers with reputable reference material for making sound clinical judgements when published clinical data is not available.

In 2016, of the 22 new molecular entities approved by the FDA, 32% received breakthrough therapy designation. This percentage is expected to increase in the future as a result of provisions included in the *21st Century Cures Act* to advance medical product innovation and ensure that patients get access to treatments as quickly as possible.

As detailed in Appendix I, I personally experienced a situation where we received a coverage request for pembrolizumab, a medication approved by the FDA under the breakthrough therapy designation to treat head and neck squamous cell carcinoma. The medication was approved by the FDA on August 5, 2016. However, three weeks later when we received our first patient coverage request,

clinical trial data was still not published and not available. We had no information available to us to determine whether the medication was appropriate for our patient and that resulted in an undue delay in her care. Had we been able to communicate with the manufacturer leading up to FDA approval of the medication, we would have had access to the data available at the time of FDA approval and been able to make a coverage decision for our patient, minimizing delays in her care.

In these situations, enabling communications prior to FDA approval is critical to ensuring population health decision makers are aware of the information available to date on emerging therapies granted breakthrough designation by the FDA so they are prepared to make coverage decisions for patients immediately upon FDA approval.

Multi-stakeholder Group Develops Consensus Recommendations for Enabling Communications Prior to FDA Approval

In September 2016, the Academy of Managed Care Pharmacy (AMCP) convened a Partnership Forum with a diverse group of stakeholders representing population health decision makers, biopharmaceutical manufacturers, patient advocacy groups, health care providers, health economists, and others. As a participant in the Partnership Forum, I worked alongside the key professionals and entities affected by the current restrictions on the sharing of preapproval information to develop consensus recommendations on how to improve patient access to emerging medication therapies by clarifying the scope of permitted health care economic and scientific information communications between biopharmaceutical manufacturers and population health decision makers, while still maintaining appropriate safeguards to prevent this information from reaching unintended entities. The full

recommendations from the Partnership Forum were published in the January 2017 issue of the *Journal of Managed Care & Specialty Pharmacy* and are also included as Attachment A.¹ The consensus recommendations from the Partnership Forum included the following provisional recommendations:

- Create a safe harbor to allow biopharmaceutical manufacturers to share truthful and non-misleading clinical and economic information about medications in the pipeline with population health decision makers proactively at least 12-18 months prior to FDA approval during the forecasting and rate setting process.
 - Forum participants agreed that a safe harbor for PIE was necessary to confirm that the proactive dissemination of certain information does not violate the prohibitions against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.
 - Forum participants agreed that information shared under PIE should meet the competent and reliable scientific evidence standard as defined by a prior AMCP Partnership Forum² to be “truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on the expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate, and valid.”
 - Forum participants agreed that the specific format or process for sharing PIE should not be prescribed in legislation but should be developed collaboratively between the

¹ Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval. *Journal of Managed Care & Specialty Pharmacy* 2017 23:1, 105-112

² AMCP Partnership Forum: FDAMA Section 114—Improving the Exchange of Health Care Economic Data. *Journal of Managed Care & Specialty Pharmacy* 2016 22:7, 826- 831

biopharmaceutical manufacturers and population health decision makers who would be exchanging this information.

- Limit exchange to narrow audience: biopharmaceutical manufacturers and population health decision makers (e.g. payors, provider sponsored health plans, pharmacy benefit managers, ACOs, and IDNs) only.
 - Forum participants debated the scope of preapproval communications and also considered whether providers and patients should be considered within scope. After much debate, forum participants agreed that given that information shared under PIE is prior to a product being deemed safe and effective by the FDA, information should only be shared proactively with those entities that have accountability for forecasting costs to ensure patient access and coverage. In addition, PIE should be limited to a sophisticated audience who has the education, training, and expertise to critically analyze and evaluate health care economic information for credibility. Therefore, PIE should be limited to a narrow audience and should only be permissible for biopharmaceutical manufacturers and population health decision makers.
- Limit exchange to new molecules and expanded indications with an intent to file only.
 - Forum participants debated whether PIE should be limited to new molecular entities only, or should also include expanded indications. During the debate, population health decision makers articulated that expanded indications can have a major impact on budgeting, forecasting, and rate setting if the expanded indication increases the patient population eligible to receive the product significantly. For example, if the indication for PCSK9 inhibitors were expanded to include generalized hypercholesterolemia, it would result in a major increase in the eligible population and corresponding costs associated

with the treatment of hypercholesterolemia. However, population health decision makers also noted that while they want to receive information about expanded indications preapproval, they do not want to receive information about all off-label uses of a product. In addition, they wanted to ensure that incentives were still in place to encourage biopharmaceutical manufacturers to file for an expanded indication as FDA approval remains the gold standard for formulary placement for most classes of medications. Therefore, forum participants recommended that PIE should be applicable to both new molecular entities and expanded indications with an intent to file. An intent to file would be demonstrated by submission of a Supplemental New Drug Application (sNDA) or other similar steps. However, forum participants also noted that in certain situations, especially for rare diseases, a financial incentive to file for an expanded indication may not be viable and therefore an avenue should be available for PIE to be applicable absent a regulatory filing in certain circumstances.

- Allow for bidirectional exchange of information that does not necessarily have to be clinical or scientific evidence.
 - Forum participants agreed that bidirectional exchange of information was a key element of PIE to encourage a continuous and ongoing dialogue between biopharmaceutical manufacturers and population health decision makers throughout a product's preapproval lifecycle. The bidirectional communication would also allow population health decision makers to share with manufacturers what they are looking for in clinical endpoints and level of evidence to make coverage decisions for patients. This notion has become increasingly important recently with the approval of new therapies for Duchenne's Muscular Dystrophy. These products were approved by the FDA as safe and effective,

but population health decision makers are hesitant to cover the products as the level of evidence does not meet their needs to make a coverage decision, resulting in patients being unable to access these products. Had PIE been permissible during the development phase of these products, population health decision makers could have shared their expectations for the level of evidence generated from clinical trials and perhaps avoided the gap in patient access that exists today.

- Forum participants debated whether PIE should be limited to “evidence” or “information.” After much debate, it was agreed that “information” was the more appropriate term as some elements shared under PIE would always amount to information and not evidence, such as anticipated indications, place in therapy, routes of administration, and budget impact. It was also discussed that economic models cannot be considered evidence and limiting the standards to “evidence” may cause legal concern and be interpreted as requiring a level of research or replicability for all information disclosed, which might be unattainable at certain stages of the product’s development.
- Forum participants discussed the need to establish a minimum set of standards that information shared under PIE should meet, including the need for a dynamic standard that would support the evolution of information to evidence as a biopharmaceutical product approaches FDA approval. Forum participants suggested that an independent objective entity comprised of a multi-stakeholder collaborative of representatives from various organizations could be responsible for developing consensus recommendations regarding good research practices for information shared under PIE. The independent objective body would also be responsible for continually updating the established good

research practices to reflect updates in scientific rigor and other advances in evidentiary standards.

- Forum participants also emphasized that because the information about a product could change and augment over time, information shared under PIE should include appropriate disclosures including transparency regarding the methods and results with appropriate disclosures of uncertainty and limitations inherent in such information.

FDA Releases Draft Guidance and Shares Its Current Thinking on Preapproval Communications

In January 2017, the FDA released a draft guidance document³ outlining its current thinking on manufacturer and payor communications. The draft guidance took a helpful first step in creating a safe harbor for manufacturer communications to payors regarding investigational products, but did not include expanded indications. While population health decision makers were pleased to see that the FDA draft guidance allows the proactive communication of certain information by biopharmaceutical manufacturers to payors prior to FDA approval, the draft guidance remains non-binding and these provisions must be codified by law. Therefore, there is a need for Congress to engage in this topic to create a legislative safe harbor for PIE so that it is clear that the proactive dissemination of certain information does not violate the prohibitions against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

³ FDA Draft Guidance - Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers [FDA-2016-D-1307]” as published in the Federal Register on January 19, 2017. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537347.pdf>. Accessed July 10, 2017.

H.R. 2026 – The Pharmaceutical Information Exchange (PIE) Act of 2017 is Introduced

In April 2017, Representative Brett Guthrie (R-KY) championed this issue by introducing *H.R. 2026 – The Pharmaceutical Information Exchange (PIE) Act of 2017* to improve patient access to emerging medication therapies by clarifying the scope of permitted health care economic and scientific information communications between biopharmaceutical manufacturers and population health decision makers. The bill, as amended, incorporates the consensus recommendations developed by the multi-stakeholder group and creates a very narrow safe harbor to allow for biopharmaceutical manufacturers to share proactively health care economic or scientific information with population health decision makers. The bill also solidifies the current thinking of the FDA and includes expanded indications, an area that the FDA did not include in their draft guidance, but an area that the multi-stakeholder group felt was integral to improving the ability of population health decision makers to properly plan, budget, and forecast for the impact of an expanded indication. The bill also requires that information provided under PIE must include a conspicuous and prominent statement describing any material differences between the information provided and the FDA-approved product labeling.

There is a Need for Congress to Engage in This Topic

PIE is an acute issue that a broad group of stakeholders came together and agreed needs clarification. While the FDA draft guidance took a helpful first step in creating a safe harbor for manufacturer communications to population health decision makers regarding investigational products, the draft guidance remains non-binding and does not provide the level of certainty needed to truly operationalize PIE. Absent a legislative safe harbor, PIE will likely not be utilized to its full potential by

biopharmaceutical manufacturers and population health decision makers for fear of enforcement, and unfortunately patients will not realize the benefits of PIE.

Therefore, there is a need for Congress to engage in this topic to create a legislative safe harbor for PIE so that it is clear that the proactive dissemination of certain information does not violate the prohibitions against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Congressional action is needed to create a safe harbor for PIE to improve patient access to emerging medication therapies.

Appendix I

In practice, the importance of the need for PIE and where access to PIE would have improved patient access to care is demonstrated in the following scenarios. The answer to improving access here is having necessary information 12-18 months ahead of FDA approval, and having legislative support that not only grants access, but provides the necessary framework and safe harbor enabling a sophisticated audience the ability to have a bidirectional dialogue concerning this information.

- (1) Scenario 1a – Hepatitis-C: All Medicare bids for 2014 benefit offerings use the 2012 experience to structure benefits offered to patients ('members'); all clinical, actuarial and cost analyses due to submit to CMS for approval 5/31/2013, including our formulary covering at least 2 drugs in every therapeutic category
 - Sovaldi: groundbreaking treatment for Hepatitis C, approved by FDA 12/6/2013 with novel mechanism; changing the landscape for an estimated 3.2 million people known to the CDC as diagnosed with Hepatitis-C (note, 7 months after we've already analyzed our costs and planned our 2014 benefits)
 - 1/1/14-12/31/14: Drugs to treat Hepatitis C accounted for \$500k (1/2 million dollars) for 4 patients in our plan. Two additional patients opted not to pick-up their medications, which would have accounted for another \$160k in spend. For that time-period, we had another 16,000 people to take care of, and cancer was the only category with higher spend.
- (2) Scenario 1b. Hepatitis-C 2014: bids for 2015 benefits due 6/2/2014 based on base period of 2013 drug use trends, Harvoni approved 10/10/2014; 2015 benefit year saw 101 claims for 32 of our

22,500 patients accounted for 10% of our spend, while only caring for 0.14% of our member patients.

In the first two scenarios, had we been able to discuss proactively with Gilead their emerging evidence, treatment options, and had a better grasp on understanding their pricing strategy for a 'cure', the restrictive coverage criteria and multiple iterations of coverage criteria revisions might not have occurred over the ensuing years.

(3) Scenario II – Oncology:

- Key timeline: follow the timeline presented previously - bids for 2016 were submitted 6/2015 & bids for 2017 submitted 6/2016 – we are always playing a game of catchup for planning and communication of benefits to our members
- Let me introduce you to a patient, one of our enrolled members – a 67 year old diagnosed with inoperable lip cancer which has spread to tongue, clinically called 'squamous cell carcinoma':
- Patient is eligible for a low-income subsidy based on annual income (annual single income $\leq 135\%$ FPL (\$16,278))
- Provider tells patient about a new treatment the FDA granted **accelerated** approval 8/5/2016 for pembrolizumab (Keytruda) to treat head and neck squamous cell carcinoma due to overall risk reduction of 16% seen in clinical trials;
- 200mg/dose every 3 weeks = plan pay \$7,178 (pt pay \$1,830)/dose x 8 visits = \$57,424 (pt pay \$14,640)/treatment course until \$6,500 Maximum-Out-of-Pocket (MOOP) Limit
- Out of pocket limits update annually, so potential for full patient liability since treatment crosses 2016-2017.

- Without being a head and neck cancer specialist, how can I have an informed discussion with my provider regarding the level of evidence showing 16% overall response rate when clinical trial evidence is not yet publicly available without a specific data request to the manufacturer?
- In this scenario if we were able to talk with the manufacturer, in this case Merck, about their pipeline and treatments ahead of time, or better yet have a portal for secure login and review the information available, thus understand their value statement and clinical data; I could better plan for this treatment and have an open dialogue with my provider once the product is approved, rather than scrambling to review the evidence and appropriateness of care on 9/1/16 when I received the request for coverage of the product and the patient already scheduled to receive treatment on 9/2/16.

Reflecting on historical ‘what if’ scenarios can only be made more impactful if we look at what is ahead:

- (4) Scenario III – Future State: In the next 12-18 months there are approximately 60 new products that have filed for, or are anticipated to file for, approval within categories including diabetes, anti-infective agents, dermatologic, inflammatory conditions, multiple sclerosis, cancer, and others.
- As a reminder, we submitted our 2018 Medicare bids for formulary and coverage criteria on June 5, 2017, and will submit our 2019 benefits and formularies the first week of June, 2018; thus each of these potential new treatments represent coverage uncertainty for payors, providers, and ultimately a patient who is at the receiving end of coverage decisions.
 - Because we can only estimate when therapies will be approved, if we receive a coverage request shortly after FDA approval, the landscape still remains one of chaos and requires special requests

to biopharmaceutical companies to access the data until the data is published, compendia and treatment guidelines are updated, and coverage criteria reflect new and novel treatments.

- These new drug application estimates do not include expanded label indications – which adds additional importance for continued communication as the label of products evolve over time as new indications are studied.

As demonstrated in my previous scenarios, each of these breakthrough therapies represent innovation and the potential to change a patient's life IF they can gain access to therapy. The barrier to access to novel therapies is a population health decision maker's ability to have sufficient data and sophisticated discussions with those most informed about the utility of the products in a timely enough fashion to plan, budget, and forecast for the therapies coming to market. Payors represent an extremely sophisticated audience who has the education, training, and expertise to critically analyze and evaluate health care economic information for credibility. These individuals are trained to review evidence and understand clinical endpoints resulting in better information applied to patient access

Attachments

Attachment A: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval.

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AMCP Partnership Forum: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval

SUMMARY

Current federal laws and FDA regulations have significantly restricted the sharing of clinical and health economic information on biopharmaceuticals that have yet to receive FDA approval. Over the past several years, organizations that make health care coverage decisions, including those that set copayments, premiums, and formulary placement, have expressed a need for receiving this information before approval, as long as appropriate safeguards exist to prevent this information from reaching unintended entities. Population health decision makers have indicated that waiting until FDA approval is often too late for the critical planning, budgeting, and forecasting associated with health benefit design, especially given the recent influx of high-cost medications and scrutiny for better evaluation and preparation. Recognizing that securities laws restrict the disclosure of nonpublic information and may need to be amended, permissible early dissemination would allow population health decision makers to incorporate clinical and economic information for pipeline drugs or expanded indications into financial forecasting for the following year's plan. Access to this information is needed 12-18 months before FDA approval when organizations are deciding on terms of coverage and budgetary assumptions for state health insurance rate filings, Medicare and Medicaid bids, contracts with health care purchasers, and other financial arrangements.

The need for exchange of clinical economic information before FDA approval was first introduced at a previous Academy of Managed Care (AMCP) forum in March 2016, which addressed section 114 of the Food and Drug Administration Modernization Act and the communication of such information after FDA approval. To address preapproval information specifically, AMCP convened a Partnership Forum on September 13-14, 2016. This forum included a diverse group of stakeholders representing managed care, the biopharmaceutical industry, providers, patients, health economists, academia, and others. The multistakeholder group represented the key professionals and entities affected by the federal laws and FDA regulations that restrict the sharing of preapproval information and the collective credibility necessary for proposing this new communication process.

Forum participants primarily focused on 6 items of discussion: (1) creating and defining new terms for how biopharmaceutical manufacturers may provide clinical and economic information 12-18 months before FDA approval; (2) defining the clinical and scientific standards that this information should meet; (3) determining which entities should have access to this information and the value to each; (4) the format and process by which this information should be disseminated; (5) developing definitions for existing terms referenced in current laws, regulations, or guidance documents that would need to be modernized to align with the identified new term; and (6) providing safeguards to prevent this information from reaching unintended entities.

Forum participants selected "preapproval information exchange" (PIE) as the correct term to describe this proposed new communication process and to be inclusive of data from pivotal phase III clinical trials, pharmacoeconomic data, and patient-reported outcomes, as well as other relevant items, including anticipated indications, place in therapy, and routes of administration. Stakeholders agreed that PIE should be truthful, non-misleading, and include a broad range of information to meet the needs of population health decision makers and health care technology evolution. Recipients of PIE would be limited to population health decision makers who need this information for coverage decisions. The format and process for PIE

disseminated should allow for a bidirectional exchange between manufacturers and population health decision makers but should not be proscribed in legislation. Furthermore, new legislative language may be beneficial, since PIE is a novel category of information. New legislation could provide a safe harbor and clarify that PIE does not violate preapproval promotion and the Federal Food, Drug, and Cosmetic Act and its regulations.

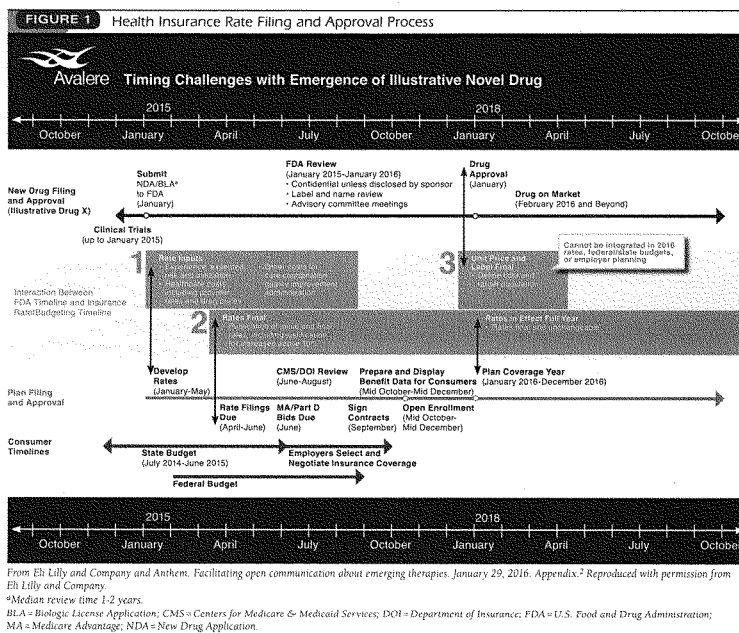
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As the U.S. health care system evolves from a historical payment system based on quantity and process to a modernized system rewarding quality and improved patient outcomes, the need for timely communication between biopharmaceutical manufacturers and population health decision makers about emerging therapies is critical for the successful shift to a value-driven system. There are 3 main imperatives driving the need for communications before approval by the U.S. Food and Drug Administration (FDA).^{1,2}

First, as a result of new laws such as the Affordable Care Act and state mandates, population health decision makers are required to evaluate their plan designs, formularies, and rates 12-18 months in advance to meet submission deadlines 6-9 months before the beginning of the intended plan year. With rates being filed over a year in advance, proper planning, budgeting, and forecasting are integral for population health decision makers to accurately account for the effect of new therapies that will enter the market. For example, for the 2016 coverage year, population health decision makers analyzed 2014 data in order to submit their 2016 rates by spring 2015 (Figure 1). The budget impact of new therapies that were approved by the FDA after spring 2015 could not be integrated into the 2016 rates. Accurate forecasting and rate setting is critical to ensure that patients have continued access to affordable coverage for their health care needs. Changes are necessary to FDA regulations to expressly permit biopharmaceutical manufacturers to proactively communicate with population health decision makers about emerging therapies before FDA approval so that more accurate forecasting and rate setting are supported, enabling affordable access for all patients to new therapies upon FDA approval.

Second, there is an increased focus on value-based payment models as evidenced by the Medicare Shared Savings Program and a range of initiatives launched and proposed by the Center for Medicare & Medicaid Innovation. Successful implementation of value-based payment models requires understanding the overall value of a therapy, including how pharmacy spending can offset medical costs and vice versa. In addition,



it requires downstream planning for population health decision makers to change plan design, formularies, and necessary contracts in advance of submitting rates at least a year in advance of the intended coverage year as previously outlined. Therefore, to increase the use of value-based payment models, it is important for biopharmaceutical manufacturers and population health decision makers to be able to share information about emerging therapies before FDA approval in order to provide sufficient time to implement these models in a timely and effective manner upon FDA approval.

Finally, the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA) created an expedited approval pathway allowing the FDA to grant priority review

if preliminary clinical trials indicate that a therapy may offer substantial treatment advantages over existing options for patients with serious or life-threatening diseases.³ Under the expedited approval pathway, therapies may be approved by the FDA before clinical trial data are published and made publicly available, thereby making it very difficult for population health decision makers to determine whether a therapy is appropriate for a patient if they receive a coverage request before publication of the data. Guidelines and peer-reviewed compendia sources are even further delayed in providing population health decision makers with reputable reference material for making sound clinical judgements when published clinical data are not available. In these situations, enabling preapproval information

TABLE 1 FDA Guidance and Other Initiatives Regarding Clarification of the Dissemination of Off-Label Drug Information

Year	Topic	Title (if applicable)
1997	Guidance on the scientific exchange of original trial results and off-label information	Industry-Supported Scientific and Educational Activities ⁴
2009	Guidance on the distribution of peer-reviewed scientific and medical publications regarding unapproved new uses of approved drugs and approved/cleared medical devices	Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices ⁵
2011	Guidance reflecting responses to unsolicited requests	Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices ⁶
2011	MIWG petition regarding clarification on off-label communication	Citizen Petition, FDA-2011-P-5012 ⁹
2013	MIWG petition requesting a constitutional response to 2011 petition (above)	Citizen Petition, FDA-2013-P-1079 ¹⁰
2014	Update to 2009 guidance	Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices ⁷
2015	Declaration that detailed the FDA's initiatives to accommodate policies to foster stakeholder interests in off-label communication	Declaration by Janet Woodcock ¹¹

FDA = U.S. Food and Drug Administration; MIWG = Medical Information Working Group

exchange (PIE) is critical to ensuring that population health decision makers are aware of the information available to date on emerging therapies granted breakthrough designation by the FDA so that they are prepared to make coverage decisions for patients immediately upon FDA approval.

Restricting Information Dissemination

Current federal laws and FDA regulations have significantly restricted communications between biopharmaceutical manufacturers and population health decision makers for emerging therapies before FDA approval, despite clear recognition that budgeting and forecasting by payers is critical to ensure that patients have access to new treatments as soon as possible following market approval. Over the past 3-4 decades, the FDA has disseminated various policy documents addressing this issue.⁴⁻⁷ While safe harbors for off-label communication already exist, the interpretation is unclear, and enforcement involves various entities with differing approaches (i.e., Health and Human Services Office of the Inspector General, Federal Trade Commission, Department of Justice, and state governments).⁸

FDA regulations ensure access to safe and effective medications, while other agencies must ensure prevention of fraud, waste, and abuse, and marketplace competition. Uncertainty regarding safe harbors and the fear of enforcement has limited the dissemination of preapproval information by manufacturers, despite population health decision makers and others expressing a strong need for this information much earlier in the drug development process. There is a definitive need to refine and clarify laws governing activities under the purview of the FDA to help diminish concerns about the possibility of legal action by other agencies. More recently, the FDA has drafted guidance to take steps to support solutions to distinct, yet related, communication challenges; granted petitions to elucidate on this topic; and announced a public hearing to review policies and clarify standards for off-label communication.⁹⁻¹¹ This topic has also been heavily discussed outside of the FDA, including at AMCP's FDAMA Section 114 forum, 21st Century Cures proposals for reform of Section 114, Biotechnology Innovation Organization and Pharmaceutical Research and Manufacturers of America's principles on responsible sharing for truthful and non-misleading information, among others (Table 1).¹²⁻¹⁴

Given these circumstances and others discussed in the following proceedings, further recommendations, guidance, and legislation are needed to provide clarity on the dissemination of information before FDA approval.

Forum Purpose and Discussion Points

To address the long-debated issue of proactive dissemination of clinical and health economic information on products before FDA approval, the Academy of Managed Care Pharmacy (AMCP) held a Partnership Forum on September 13-14, 2016, in Tysons Corner, Virginia, with a diverse group of health care stakeholders to provide recommendations for Congress and the FDA. The purpose of this forum was to discuss the following 6 items:

1. The term that would be used to describe the ability of biopharmaceutical manufacturers to proactively share clinical and economic information about medications in the pipeline with payers and other entities before FDA approval.
2. The standards that clinical and economic information should meet before FDA approval.
3. Stakeholders who should have access to clinical and economic information before FDA approval and the value of this information to each of these entities or individuals.
4. The preferred format and process by which eligible entities would like to receive clinical and economic information from biopharmaceutical manufacturers before FDA approval.
5. The definitions for existing terms referenced in current laws, regulations, or guidance documents (i.e., labeling, misbranded, or intended use) that would need to be modernized to align with the identified new term for the exchange of clinical and economic information before FDA approval.

AMCP Partnership Forum: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval

TABLE 2 Summary of the AMCP FDAMA 114 Partnership Forum¹²

Objective	AMCP convened a Partnership Forum for stakeholders to discuss clarification and possible expansion of FDAMA Section 114 to obtain consensus recommendations on how information related to this statute should be disseminated.	
Key stakeholders	Pharmaceutical industry, managed care industry, health care providers, pharmacoeconomic experts, health policy experts, and patient advocates	
Recommendations: Terms, Definitions, and Key Points		
Term	Definition	Key Points
Competent and reliable scientific evidence	"Truthful and non-misleading tests, analyses, research, studies, models, or other evidence. Such evidence would be based on the expertise of professionals in the relevant area and be derived using methods that are transparent, disclosed, reproducible, accurate, and valid."	Models would be left behind with reproducible methods.
Formulary or other similar entity	"Health care decision makers beyond health plan formulary committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations."	<ul style="list-style-type: none">• "Other entity" needs to be flexible as the health care industry evolves over time.• The role of the individual needs to be a key consideration.• Inclusion of patient advisory groups was debated, since some of these groups are sophisticated and have the ability to interpret this information, but not all do, so proper protections need to be considered.
Health care economic information	"Any analysis that identifies, measures, or compares the economic, clinical, or quality of life consequences for any treatment. This includes the costs and resource utilization of a drug or health technology relative to another drug, health technology, or no intervention."	Includes noneconomic information as well, since clinical and quality life endpoints are a part of economic evaluation.

AMCP=Academy of Managed Care Pharmacy; FDAMA=Food and Drug Administration Modernization Act; HCEI=health care and economic information.

6. The public health protections that should be considered to prevent the dissemination of clinical and economic information to unintended entities before FDA approval.

AMCP previously held a Partnership Forum in March 2016 to address communications of health care economic information (HCEI) after FDA approval. More specifically, the March forum discussed the clarification and possible expansion of Section 114 of the Food and Drug Administration Modernization Act (FDAMA) to obtain consensus recommendations on how information related to this statute should be disseminated.¹² While the recommendations from the March forum (Table 2) were focused on HCEI dissemination after FDA approval, a key recommendation was that further discussion was warranted to create recommendations for information exchange before FDA approval.

Stakeholders participating in the September Partnership Forum on preapproval communications were separated into 3 groups. Throughout the forum, each group, which was composed of representatives from the biopharmaceutical industry, payers, provider organizations, academia, health economists, and patient advocacy groups, among others, began its discussion with the question of whether the recommendations from the March forum on post-FDA approval communications were applicable to pre-FDA approval communications or whether the latter required adjustments given the differences in purpose and use before versus after FDA approval. The following recommendations and discussion points are reported to reflect where there was agreement, and where further discussion is warranted.

Terminology to Describe the Sharing of Preapproval Clinical and Economic Information

When considering the terminology that should be used to describe the ability of biopharmaceutical manufacturers to proactively share clinical and economic information about medications in the pipeline with payers and other entities before FDA approval, debate among the 3 groups focused on 3 areas: (1) the term "preapproval," (2) whether the information to be communicated should be information or evidence, and (3) whether the method of conversation should be deemed an exchange or information sharing.

Preapproval

The groups discussed the need for a term that is narrow enough to be included in legislation or adopted in guidance. Whether to include "preapproval" in this term was debated. Stakeholders reached consensus that the final recommended term should differentiate what type of information is to be shared. Including the word "preapproval" in any such term would highlight that the term refers to information disclosed for forecasting, planning, and budgeting before FDA approval. A key point of discussion was when pricing information would be available for medicines initially entering the market. Some stakeholders noted that pricing may only be known shortly, if not immediately, before product launch, while other stakeholders expressed an interest in receiving pricing information, or at least a range of possible prices, as early as possible. Stakeholders recognized, however, that manufacturers must

comply with securities and trade secrets laws that restrict the dissemination of material nonpublic information, which could include pricing, as well as certain clinical trial data.

Information Versus Evidence

The terms "information" and "evidence" were used to describe the clinical and economic data to be communicated. Although the term "scientific information" was proposed, stakeholders agreed that this term may be misinterpreted as being limited to research studies subject to scientific rigor, when instead, the proposed term should be inclusive of additional purposes (e.g., identifying potential patient-populations, distribution requirements, and budgeting). Some stakeholders indicated that as biopharmaceuticals move through the early phases of development, information builds over time and eventually leads to a body of evidence in the later phases of development and throughout the product life cycle. Furthermore, the term "information" was deemed appropriate by some because "evidence" may be viewed as only the types of data that involve a statistical comparison and may limit the use of models and valuable cost analyses. Stakeholders expressed that models cannot be classified as evidence, since they are simply tools to develop estimations, and there was a strong concern among many stakeholders that deeming a model as evidence would lead to misinterpretation as to what such models can and cannot demonstrate and depict from a level of certainty. Those who supported use of the term "evidence" stated that "information" is a broader and more encompassing term that may not have as much weight in the scientific community. The concept of information versus evidence is discussed in more detail throughout this proceedings document.

Exchange Versus Information Sharing

The third area of discussion focused on the terms "exchange" versus "information sharing." Supporters of the term "exchange" felt that the use of this term would signify bidirectional conversations between decision makers and manufacturers and reinforce an ongoing dialogue between the 2 parties. Proponents of the term "information sharing" thought that the term "exchange" would be confused with scientific exchange, which has traditionally been interpreted to be applicable to investigational new drugs under 21 CFR 312.7(a) and therefore expressed hesitance in using this term.

After thorough discussion, stakeholders agreed on the term "preapproval information exchange" (PIE), which referred to the proactive sharing of clinical and economic information by manufacturers to decision makers (entities are discussed later in the proceedings) at least 12-18 months before FDA approval and the ongoing discussions between the 2 sharing entities as information evolves into evidence throughout drug development. Furthermore, stakeholders agreed that this preapproval communication only applies to those

biopharmaceutical manufacturers who intend to file for a new indication (new molecules and new indications), thereby limiting the risk for off-label promotion. Stakeholders agreed that the intent of a biopharmaceutical manufacturer to file would need to be justified by submission of an Investigational New Drug (IND) application, New Drug Application (NDA), Supplemental New Drug Application (sNDA), or other similar steps.

Standards for Preapproval Information

Discussion on the question "What standards should clinical and economic information shared prior to FDA approval meet?" began with the definition of "competent and reliable scientific evidence" as developed in the FDAMA 114 forum (Table 2) and how to differentiate the preapproval setting from the postapproval setting. Overall, stakeholders agreed that the standards for this information should be based on the FDAMA 114 forum definition, with a few proposed exceptions:

- "Information" should be either added to the definition or should replace "evidence."
- A minimum set of standards should be set for this information, but as a biopharmaceutical product approaches approval, the information would become stronger and evolve into evidence.
- It was emphasized that because the information about a product could change and augment over time, any disclosure of information for PIE purposes needed to include transparency regarding the methods and results (all of which would need to be done in a truthful and non-misleading manner) with appropriate disclosures of uncertainty and limitations inherent in such information, and methods would need to be reproducible—not the results).

Some stakeholders expressed that all-inclusive information sharing, with ultimately no restrictions, may allow too much lenience, while being too specific may inhibit manufacturers from sharing important information with population health decision makers that would be of value to their decisions and ultimately be important for planning and forecasting purposes. As mentioned in the previous section, limiting the standards to "evidence" may cause legal concern and be interpreted as requiring a level of research or replicability for all information disclosed, which might be unattainable at certain stages of the product's development, whereas the intent is to be able to include additional items such as anticipated indications, place in therapy, routes of administration, distribution channels, and potential budget impact.

Entities and Individuals Who Should Receive Preapproval Information

During the FDAMA 114 forum, it was decided that entities who should receive HCEI after FDA approval would be "health care decision makers beyond health plan formulary

committees, including organizations, or individuals in their role in an organization, who make health care decisions for patient populations and organizations that evaluate HCEI or develop value frameworks and compendia, including individuals in such organizations" (Table 2). Stakeholders were asked to consider these same entities for preapproval purposes, in addition to pharmacy and therapeutic committees, managed care pharmacy, health care providers, accountable care organizations (ACOs), integrated delivery networks, patient advocacy groups (PAG), organizations that develop value frameworks (e.g., American Society of Clinical Oncology and National Comprehensive Cancer Network), organizations that develop clinical practice guidelines (e.g., American College of Cardiology and American Diabetes Association), research societies (e.g., International Society for Pharmacoeconomics and Outcomes Research), actuaries, contract specialists, and others.

All stakeholders agreed that population health decision makers such as managed care organizations and pharmacy benefit managers would be eligible to receive preapproval information. In addition, certain integrated delivery networks (IDNs) and ACOs that bear financial risk for biopharmaceuticals would also be eligible to receive preapproval information. These population health decision makers were included because entities and individuals within these organizations need to receive this information in advance of FDA approval for budgeting, forecasting, and coverage decision purposes.

Forum stakeholders also considered whether other entities that are "influencers," such as groups that develop value frameworks and clinical practice guidelines should be included in PIE. Some stakeholders thought that clinical practice guidelines developers would need to know this information, since the evolution of guidelines is a lengthy process, and it would be beneficial to know this information for the next guideline update. A limited number of stakeholders thought that some benefit exists in expanding this information sharing to PAGs, since the FDA is moving toward more patient-focused drug development. However, the majority of stakeholders strongly argued that the need for HCEI is for entities that have accountability for forecasting costs to ensure patient access and coverage, which is not the case for influencers or PAGs. While preapproval information sharing with influencers and PAGs was considered, there was consensus that the pre-FDA approval information most valuable to influencers and PAGs was clinical in nature, not preliminary economic or financial data. Furthermore, entities such as influencers or PAGs could receive this information through the usual channel of unsolicited requests. Therefore, the majority of stakeholders agreed that only entities who manage a population's health should receive preapproval information.

Preferred Format and Process for Receiving Preapproval Information

After reviewing the recommendations set forth at the FDAMA 114 forum, stakeholders were asked the question "What is the preferred format and process by which eligible entities would like to receive clinical and economic information prior to FDA approval from biopharmaceutical manufacturers?". Overall, stakeholder consensus supported the creation of a flexible means of providing this information that allows for a bidirectional exchange between manufacturers and population health decision makers and that a specific format or process should not be prescribed in legislation. Furthermore, AMCP was identified as a potential driver and leader in this space, given that AMCP has an established process for communication of information about biopharmaceutical products to inform decisions made by formulary committees. This process is currently restricted to unsolicited requests but could be adapted for PIE. Conversely, a few key points were debated:

1. *Central repository versus repositories for each manufacturer.* Some stakeholders thought that having multiple repositories (each for a different biopharmaceutical manufacturer) would simplify the risk of unintended users gaining access to preapproval information. Others stated that having the ability to compare medications and technologies in a central repository during a single log-in would allow for a more simplified, effective process. The central repository would allow for alerts once information is updated—decision makers could choose to opt-in and the frequency of the alerts they would like to receive (e.g., once a month or once a week). Later in the discussion, stakeholders noted that AMCP already has a central repository system in place for dossier submissions and viewing; therefore, this same system could be adapted as an option for communicating information in the preapproval setting.
2. *Standardized format versus flexible format.* An AMCP dossier-light format was initially suggested by many stakeholders, while others were concerned that not all end users, such as IDNs and ACOs, would be as familiar with this format; therefore, the format would need to be adaptable and flexible to suit the needs of organizations or entities. Furthermore, technology is rapidly evolving and developing, so a format developed today may not be useful tomorrow. Others disagreed, stating that a standardized format with the ability to locate the same information in the same location between 2 products would allow for a more simplified, consistent process.
3. *Communication and notification.* Communications via a repository would include notifications to decision makers once information was updated, options for manufacturers to share models and slide-decks, and one-on-one conversations between manufacturers and decision makers. More importantly, manufacturers and decision makers would have the option to choose the type and frequency of

engagement, depending on their individual needs, and whether to use a central repository or another process for exchanging this information.

Stakeholders ultimately agreed that the forum discussion is a starting point for the consideration of format options and that a specific format or process should not be prescribed in legislation but should be developed collaboratively between the manufacturers and population health decision makers who would be exchanging this information. The group agreed that given AMCP's history of providing this type of information, it is in a good position to serve as a leader and developer for providing information under PIE.

Definitions for Existing Terms in Current Laws, Regulations, or Guidance Documents

Given the existing terms included in current laws, regulations, and guidance documents, stakeholders were asked the question "How should the definitions for existent terms, referenced in current laws, regulations, or guidance documents (such as labeling, misbranded, or intended use) be modernized to align with the identified new term for the exchange of clinical and economic information before FDA approval?". Stakeholders quickly reached a consensus that PIE would need to have its own safe harbor, in a manner consistent with existing law.

Public Health Protections to Prevent the Dissemination of Preapproval Information

Stakeholders considered the public health protections required to prevent the dissemination of preapproval information and agreed that it should function similarly to the system in place for HCEI under FDAMA Section 114. The stakeholders agreed that certain public health protections are already in place through other legislation, so there may not be a need to create further protections beyond those already enacted.

Conclusions

Currently, the sharing of clinical and health care economic information on new products and indications before FDA approval is significantly restricted by federal laws and FDA regulations regarding product promotion. Population health decision makers have expressed a need for receiving this information at least 12-18 months before FDA approval to properly plan, budget, forecast, and care for the populations they serve, as long as safeguards are in place to prevent preapproval information from reaching unintended entities. The recommendation from this Partnership Forum is for Congress to establish a safe harbor for preapproval information exchange between biopharmaceutical manufacturers and population health decision makers to encourage better decision making, without interfering with innovation in the biopharmaceutical and health technology industry.

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Mr. BURGESS. I thank you for your testimony. I want to thank all of our witnesses. It has certainly been compelling testimony this morning. People will note that I allowed the clock to run over because you had important information to provide us. I guess we will underscore that I will not be so generous with Members, so try to confine your time to the 5 minutes allotted to these products that have not been evaluated by the FDA. This product is not intended to diagnose or prevent any condition, just to get through the appropriate label disclaimer.

Let me begin the questioning and I will recognize myself for 5 minutes. And Ms. House and Ms. Khachatourian, thank you so much for your testimony.

Ms. House, while you were talking and I actually wrote down a note to myself about when you mentioned about clinical trials and I was going to ask you about the utility of getting the information off of clinicaltrials.gov and then Ms. Khachatourian actually referenced that as well. So this is a real-world phenomenon where payer decisions are unable to be made, but the data is sort of accumulating on the data side of the docket, but it is not coming up to the payer's side. So it sounds like both of you have dealt with that.

And Ms. Khachatourian, I thank you for bringing up the issue with the new hepatitis C drugs, because we were sitting on these panels in 2012 and 2013. And I would suggest it is not just an issue of commercial payers. Our State Medicaid directors, our State prison directors, our Federal prison directors were going to have to deal with this information in very short order and they did not have it available to them.

And I would be happy to listen to what both of you have to say, particularly on the clinicaltrials.gov. Are we doing a good enough job getting that information out there in a usable way so that you can actually begin the process of what are we going to have to do as far as on the payer's side?

Ms. House, we will start with you, and then I would like to hear Ms. Khachatourian's thoughts on that.

Ms. HOUSE. Thank you, but I didn't share my comments that I have in my written testimony. I included two studies that were done on the clinicaltrials.gov database where there was a random sampling of 600 trials originally. And 50 percent of those trials did not have a corresponding article. The second study was even more alarming in that there was a look at 13,327 trials and 1-year post-data closure, only 13 percent of those has posted clinical trials information. And even when they gave a bit of a grace period and extended that for another couple of years, only 38 percent had clinical trials posted there. So not only is the system extremely difficult to sort of use and find and especially as we are moving into the age of personalized medicine to get to trials that are relevant for me, the data results aren't there.

And I will give you an example that happened to me just last week, is that a patient of ours reached out and he has a certain type of lung cancer, ALK positive lung, in which there are a number of solutions and options available for him. His physician wanted to put him on a phase 2 trial with a new product and he said, "What do you think about this?" And so I went online to try to find

information because I was trying to decide why would they put him on a phase 2 trial instead of the phase 3 trial, and I am an educated consumer and I have worked in clinical trials for a long time. After about an hour and a half, I could find two sources online to your point. One of them was with a reputable medical society and the other was an opinion piece on the way in which this product worked.

They are in a phase 3 setting already, so there is a lot of evidence on this particular drug and not available to even educated consumers.

Mr. BURGESS. OK. Ms. Khachatourian.

Ms. KHACHATOURIAN. Thank you, Mr. Burgess. I actually pulled some dates more relevant to some recently approved therapies. In the hepatitis space, the products Zepatier and Epclusa were approved January 28, 2016, and June 28, 2016, per the FDA website. However, results on clinicaltrials.gov were not published until September 27, 2016 and April 26, 2017 respectively. So just to give perspective regarding when data is available and results are published, those are key dates that I was able to glean. I have some oncology examples as well, but I think that proves the point regarding the delay in access to information that is necessary for coverage decisions.

Mr. BURGESS. Dr. Van Hare, you referenced the rich data sets that would be available by a drug or device manufacturer, but that data is sort of locked away from the clinician. I guess you have to go the bar to have those discussions? You can't have those discussions in the hearing room or the continuing education room? You have to go offsite?

Dr. VAN HARE. On the stairwell.

Mr. BURGESS. On the stairwell, OK. Very well. And you see what we are talking about today as a way of unlocking those data sets being available to the clinicians?

Dr. VAN HARE. I think so. I think it is really pretty simple for allowing off-label use. A physician who prescribes something off-label is responsible for ensuring that they have evaluated the most appropriate clinical data before they make a decision about prescribing something off-label and some of that data is actually held by the manufacturers.

They are allowed, as I understand it, to provide it to us privately and in response to an unsolicited request, but you know, there is 300 of me in the country, the pediatric cardiologists who do what I do in the country. Every single one of us has to independently call up the drug company to get the information. It is not particularly efficient.

Mr. BURGESS. No. I think my time is expired. I want to be respectful of everyone's time.

Mr. Green, you are recognized for 5 minutes for questions, please.

Mr. GREEN. Thank you, Mr. Chairman. Long ago, Congress recognized the importance of requiring manufacturers to provide evidence demonstrating the safety and efficiency of the product. In marketing under current law, drug and medical device manufacturers can disseminate certain medical and scientific information

about unapproved uses of approved or cleared products to health care professionals and other entities.

Recent court cases cited as a source of uncertainty around the types of communication about these unapproved uses are permissible.

Ms. Charo, in your written testimony, you said if the First Amendment means that the off-label promotion must be permitted, then the promotion of entirely untested, unproved drugs should also garner the same protection. Is that true?

Ms. CHARO. I fear that the logic would be the same in both cases. Now it is true that for things that have been approved at least once, one does have some, at least, early information that the drug is not highly toxic because that is what we are going to get from the early Phase 1 or 2 trials. But the reality is over time, both the drugs that have never been approved before or the off-label indications for things that have been approved turn out to fail which means that one begins with a presumption that any unapproved use or any unapproved drug is probably not safe or not effective until it is proven to be so.

Mr. GREEN. Well, this is an issue that this subcommittee and our committee has wrestled with for a number of years. Can you help us understand what restrictions the Constitution does and does not allow? Does the First Amendment prohibit the FDA from restricting promotion of unapproved uses?

Ms. CHARO. No, there are a number of Federal cases that have upheld the FDA's authority to do just that. There is constitutional protection for commercial speech and there are standards for that protection and in the area of commercial speech it is a fair amount of protection although not the same degree of protection as you would get for political speech or other forms of speech. And those restrictions on commercial speech are permitted when there is a substantial public interest in doing so. In this case, by restricting off-label promotion, one is able to create both a stick and a carrot that drives the pharmaceutical industry toward the research needed to actually figure out which things are safe and which things are effective. If one is able to simply promote without restriction and gets no market advantage by going in and investing in the research, one loses that system entirely and we really do risk having an absence of information for people like Dr. Van Hare to solicit or to develop on his own, let alone to share with his colleagues.

Mr. GREEN. Ms. House, I note in your focus on your testimony the fact that so much clinical trial data is unpublished. One thing that concerns me is the bias in what is published. Multiple studies have shown that positive trial results are more likely to be published than negative results. And in particular, industry sponsorship has been demonstrated to be a factor contributing to the biased publication. Industry has no incentive to publish or promote negative findings.

My question is if industry is more likely to publish positive than negative results, do you also worry that positive results will be promoted more than negative results, even if there is a particular research being communicated is truthful and not misleading? Doesn't selected provocation create a distorted view of the safety and effectiveness of the unproven use?

Ms. HOUSE. I am going to answer this very carefully because I have not seen the data that you're referencing that would suggest that there is more positive data than negative data. What I would say is that our position is that both positive and negative data needs to be published in an equal manner and should be available for communication because we do know that there are patient harms as well as benefits.

Mr. GREEN. And I think that is what we want to get to. If I am a pharmaceutical or if I am advertising anything else, I am going to talk about how great it is. If we are running for office, I am not going to talk about our bad side. We are going to talk about the good side. So we need to have it, but we need some agency to be able to say this is what you are doing and the FDA is what we have. That is my frustration, I guess.

Dr. Van Hare, in your testimony you note that Pediatric Research Equity Act has not been sufficient in producing the amount of shareable data we might like particularly in the older drugs and clinical decisions are often made. I think you raised an important point about the need for the robust data to allow clinicians to make the best decisions they can. My concern is there is nothing in this legislation we are talking about today would actually encourage drug companies to conduct those clinical trials that could answer important questions for pediatric populations. And again, our subcommittee for decades has wrestled around what may be appropriate for an adult is just not appropriate for children and we need to do a lot more work on that to make sure that we don't leave out the pediatric population.

Mr. Chairman, I know I am over time, so I yield back my time, unless you want to give it Dr. Van Hare?

Mr. BURGESS. Dr. Van Hare, did you want to comment?

Dr. VAN HARE. I think that legislation has actually helped children in terms of getting a lot more information about drugs. And certainly in the pediatric world, originally for some companies or actually enticed some companies to actually do some trials. For the most part though companies are not really interested in the pediatric market. We are very, very small market and sort of thinking about the carrot and stick sort of approach, none of the carrots are really going to help us in pediatrics because it is a fairly small market. So we are left in a situation where no one is going to do the type of clinical trial that was actually going to allow labeling for pediatric application for a lot of the things that we actually use.

Despite that, we are talking care of our children, and we need the best available data to make those decisions.

Mr. BURGESS. Thank you. The Chair recognizes the gentleman from Illinois, Mr. Shimkus, 5 minutes for questions, please.

Mr. SHIMKUS. Well, thank you. I am going to follow up with Dr. Van Hare first of all saying for my colleagues that the Washington University School of Medicine is one of the preeminent institutions in our country. And VJC which they are affiliated with, that is the go-to for major deals. So welcome.

Dr. VAN HARE. Thank you.

Mr. SHIMKUS. And I know that because—please extend my hello to Dr. Braverman and Dr. Damiano, who I know personally from personal medical stuff. I am a Homer for these folks and I have

great confidence in your testimony and your word. But I would like to follow up on the question in that how often do you assess the various information to try to treat kids? I mean so we are talking about FDA approval, but you have given testimony about outside information to make sure you can best care for kids. How often do you go and search outside information to try to bring the best medical care to the kids in the cardiology aspects?

Dr. VAN HARE. It really depends on what the condition is that we are actually trying to treat. I would say that we do have the process of developing consensus documents that actually summarize the medical evidence, the clinical trials and things like that that actually sort of express and certainly our society, the Heart Rhythm Society does this all the time to create these consensus documents to give physicians guidance. But you know, I guess pediatrics and also really sub-specialty medicine in general, we take care of a lot of very unusual types of conditions that don't really fall under the labels and the recommended uses. And so I guess for those less common, more unusual types of situations, we are often looking to our colleagues. We are calling around. We are finding what has your experience been with this? What has your experience been with that?

Interestingly, I am a real proponent of the concept of partnership between industry and physicians. We often work elbow to elbow when we put pacemakers in and when we do different kinds of procedures. They have a lot of information just from their experience and it is an important source for us.

Mr. SHIMKUS. Great. Thank you. Let me go to Ms. Klasmeier. In your testimony you talked about, and I quote, "strict scrutiny" the test. What does that mean, strict scrutiny in a test in court?

Ms. KLASMEIER. As a practical matter, Congressman, it means the government loses. So strict scrutiny is a bit of a legal fiction that we indulge. It reflects the notion that when you examine Government regulation that affects core speech such as political speech, it is very, very hard for the Government to sustain its burden of justifying that speech regulatory provision against First Amendment is solvent. So as a practical matter, if the court concludes the applicable standard is strict scrutiny, the Government loses.

Mr. SHIMKUS. Maybe my colleague, Mr. Griffith, will follow up on that. He is our legal mind here on the committee and does a good job.

Let me finish with Dr. Kesselheim. I am somewhat confused in your testimony because you used numerous times the term promotion over and over again in your testimony. But on page 2 of the Griffith draft, it explicitly excludes promotional communications. Am I missing something?

Dr. KESSELHEIM. Well, no. I mean I think this is part of an example of how the Griffith draft actually makes something that is fairly clear a lot less clear because, you know, if the pharmaceutical company defines something as promotion determines whether or not they fall into this safe harbor.

Mr. SHIMKUS. What do you mean by promotion? You used it numerous times.

Dr. KESSELHEIM. Sure. When a pharmaceutical company promotes a drug, it goes out and it tells people about the use of the—

Mr. SHIMKUS. For their ability to sell it?

Dr. KESSELHEIM. Yes. It goes out and it tells physicians about how to use the product and it sort of promotes the use of the drug through one of the various advertising—

Mr. SHIMKUS. I am reclaiming my time. I will let Congressman Griffith kind of hash this out more, but again, on page 2, it is pretty clear. It says communication is not advertising or otherwise promotional in nature. So I just had a concern with your statements in your opening statement because you said it over and over again. I think it gives the wrong indication of what my colleague is trying to do. With that, I yield back my time.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back. The Chair recognizes the gentlelady from Illinois, Ms. Schakowsky, 5 minutes for questions, please.

Ms. SCHAKOWSKY. Thank you. I think it is really important that we step back and remember that the FDA approval process really is the gold standard, the universal gold standard to determine safety and efficacy. And efforts to undermine that standard are very worrisome to me and I think that is what happens in these drafts. I think that Ms. Charo put it best in her testimony when she stated “for complex products like drugs, the marketplace of ideas cannot work properly with unvetted information from a self-interested source.”

I mean I think that often this committee is inclined to say whatever PhRMA wants, PhRMA gets. But I want to ask Dr. Kesselheim, we have heard compelling testimony, I think, about access for patients to drugs. And so it is very important, I think, for you to explain what—does access trump safety or does it have to by having these kind of off-label procedures? It seems to me that safety ought to come first, but are there ways to guarantee that safety without the process of approval by the FDA?

Dr. KESSELHEIM. Well, I mean so sure and I think that part of some of the testimony that we heard was a little bit disingenuous because the access to the products was not defined necessarily by the communications that occurred. The access in the case of the hepatitis C drugs, the effectiveness of the hepatitis C drugs is not a secret. Everybody knew how well they worked. Access to them was determined by the high cost of the product, not the evaluation, not whether or not there could have been communication in the few months before the drug was approved. So I mean I think the issue is really about getting high quality evidence or high quality communications out to help inform the market so that patients can make well-informed decisions based on the highest quality information that is out there possible. And the way to do that is to make sure that a neutral, third party body of experts like the FDA is able to vet the information. And I think what we should be doing is talking about how to make sure that more information is published, more trials are published, more trials are available, open access, and that the FDA has more power and more authority to review information so that they can make those kinds of determinations so patients can benefit.

Ms. SCHAKOWSKY. Is there a way for the FDA to move more quickly? We heard about 9, 10 years, or whatever?

Dr. KESSELHEIM. I think if the FDA had more resources, it would be able to move more quickly. There are plenty of examples where the FDA has gone out and has been concerned about new safety issues that emerge, about off-label uses and ultimately goes through the process of revising the label to try to integrate those kinds of changes. If the FDA had more resources added and more people doing that kind of post-market surveillance, label updating kind of work, then I think we would get that information out to patients and vetted information out to patients more efficiently and more quickly.

Ms. SCHAKOWSKY. Ms. Charo, one of the most compelling things I heard from you saying that, in fact, when you look at these drugs, the majority of them, in fact, would probably not meet the test. Am I hearing you right?

Ms. CHARO. You are hearing me correctly, and I believe, in fact, it was Ranking Member Green who referenced some of those studies in his opening comments.

You know, scientific research is often somewhat equivocal for a very long time. I think what we are discussing here is really what to do in that interim period where the evidence is shifting around. Do we presume everything is going to work and therefore everything people want to say is likely to be true and should be allowed or are we going to presume that it probably isn't going to work out and we should restrain the speech until we have actually proved it will.

From my perspective, given that the risk of incorrect information is that people will actually be harmed, or they won't go for the effective treatment, they will go for the ineffective one, we need to err on the side of caution here and protect the larger population.

That said, there are certainly going to be some occasions in which it turns out that something does work and it would have been wonderful if we could have seen it earlier and talked about it earlier, but those incidents will be fewer than those in which it would be damaging.

Ms. SCHAKOWSKY. In the last 30 seconds, Dr. Kesselheim, what does history tell us about off-label promotion? Are there some things we should be recognizing here?

Dr. KESSELHEIM. Sure, I mean over and over and over again throughout history and you don't even have to go back to the thalidomides 50 years ago, more recent history tells us that off-label promotion drives physician practices in ways that favor the drug being promoted, not in ways that favor the overall state of the evidence and the overall state of practice. I think that we need to be very wary about efforts to try to expand that promotion when it covers nonevidenced based—potentially nonevidenced based communications.

Ms. SCHAKOWSKY. I think we need to, when it comes to patient access, discuss more about the cost. Thank you.

Mr. BURGESS. The gentlelady yields back. The Chair thanks the gentlelady. The Chair recognizes the gentleman from New Jersey, Mr. Lance, 5 minutes for questions, please.

Mr. LANCE. Thank you, Mr. Chairman. Let me state that I don't believe any of the testimony has been disingenuous, in my judgment. This is a very difficult issue, and we are trying to balance the equities on this committee, and I am pleased that every member of the panel is here, and I do not question the integrity of any member of the panel.

Counselor Klasmeier, do you believe that the standard will be strict scrutiny, or will it be rational basis, or will it be some intermediate standard, based upon your professional judgment as a distinguished member of the bar?

Ms. KLASMEIER. Congressman, my judgment is that the standard will be some variation of intermediate scrutiny.

Mr. LANCE. Intermediate scrutiny, yes.

Ms. KLASMEIER. And it will be most likely the Central Hudson standard with a garnish of heightened scrutiny as a result of the Supreme Court's decision in Sorrell in 2011.

Mr. LANCE. Yes, that is my judgment as well, and I think that there is a history of decisions in this regard that would indicate that that is probably where we would be eventually as a matter of legal analysis. Thank you.

Dr. Van Hare, we have all heard that some off-label uses are well established in clinical practice, and supported by high-quality evidence, and are the standard of cure for many conditions. From your perspective, based upon your distinguished history, how does the pieces of legislation before this committee stand to improve care for patients?

Dr. VAN HARE. Well, to the extent that the legislation proposed by Congressman Griffith allows or improves the efficiency of sharing data that the device companies and pharmaceutical companies actually have, for physicians who are prescribing off-label, I think it will actually help.

Mr. LANCE. Thank you, and other members of the panel are certainly welcome to comment.

Ds. Khachatourian, what are the odds that if we pass legislation we are considering today, sophisticated population health decision makers like payers, provider sponsored health plans, pharmacy-benefit managers, and other organizations would be misled by unscrupulous drug and device manufacturers who make unfounded claims about their products?

Ms. KHACHATOURIAN. So first let me acknowledge my testimony by no means disingenuous.

Mr. LANCE. I am sure and that is why I raised it. And if I might interrupt you, I try to lead by example in the Congress, both on the floor and in committee, and I enjoy the testimony of every witness who comes before us. Those who know me know that disingenuous is not a word that I find attractive in vocabulary here on Capitol Hill. Yes, please continue.

Ms. KHACHATOURIAN. Thank you. So population health decision makers and clinicians that we are discussing here are well trained to look at things with scrutiny and to determine what level of evidence is acceptable. And during the multi-stakeholder discussions that we have had, we did address the need to determine a level of evidence and to have an agreement on what is acceptable and non-misleading. And as evidence continues to evolve and as new thera-

pies continue to emerge, that is the goal, is to develop strict criteria that will be used to apply to any level of evidence in order to ensure that it is high level and with the patient's best interest in mind.

Mr. LANCE. Certainly, and that is what we are attempting to get to a place where we can make sure that always there is the greatest standard of care. It is the jurisdiction of the subcommittee and ultimately of the full committee to promote the better health of the American Nation, and we recognize this is a difficult issue and I certainly commend my colleagues, including the gentleman to my immediate right, the distinguished Member from Virginia, as we undertake an analysis of how best to protect the American people recognizing that that is the goal of this subcommittee in a bipartisan nature. I yield back 22 seconds, Mr. Chairman.

Mr. BURGESS. The Chair thanks the gentleman. The Chair recognizes the gentlelady from California, 5 minutes for questions, please, Ms. Matsui.

Ms. MATSUI. Thank you very much, Mr. Chairman. This committee recognizes the important role that FDA plays to ensure public health and safety as evidenced by the bipartisan User Fee Reauthorization that we intend to pass out of the House this afternoon.

Now we can't tolerate efforts to jeopardize that role as patients across America who take drugs to treat or cure conditions rely upon the FDA to monitor the safety of these drugs and devices.

I am really glad that we are holding this hearing today to examine issues that arise around information sharing, particularly for those so-called off-label use and what could be done to alleviate those issues without detracting from FDA's ability to regulate safety.

I am particularly interested in the situation that many rare disease and cancer patients find themselves in. As many as one in five prescriptions are written for drugs off-label, meaning that they are prescribed for a condition or population that has not been FDA-approved as safe and effective. Oftentimes, off-label drugs are the only treatment available and even the standard of care for rare disease patients with limited options.

Ms. HOUSE, thank you very much for your advocacy on behalf of cancer patients. Can you please discuss prevalence of off-label use in cancer patients?

Ms. HOUSE. So there was a physician posted by the Friends of Cancer Research just yesterday that indicated that the use in cancer off-label was close to 80 percent. And part of—one of the problems that I just wanted to raise is I was looking at some other discussion is I am going to give you an example. It is an older example, but it really talks about how the current labels are out of date. There was a time around 2000 where this is the time prior to personalized medicine, so it was still in the era of poisons for cancer, that there was a combination being used off-label as standard of care for the treatment of lung cancer. That particular combination failed at that time 13 Phase 3 trials which is the gold standard for the evaluation for the FDA, yet it continued to be used standard of care for many, many, many years beyond that.

This morning, I went on the FDA website and pulled up the label for the lead drug in that and today in 2017, still has not been updated to reflect the use of that combination which is a problem.

Ms. MATSUI. It is a problem, right. Now, you know when a family gets a cancer diagnosis, I think the world stops. And you are sort of grasping at what can we do? And I think we all go to the internet. That is where we go right now.

What types of information is generally available to patients and their providers when a drug is used off-label and even when you are an educated consumer, you really kind of hit a brick wall. What kinds of solutions might you recommend to address these challenges?

Ms. HOUSE. I think creating solutions that again are tailored to the stakeholder, to their literacy level, to their educational level. There is really no reason why we can't create forums that would be peer reviewed, scientifically sound analysis, and presentation of clinical data. What it does prevent then is people going to the internet and getting into a chat room that may be facilitated out of another country or by somebody who has absolutely no medical background. And we see that happening all the time. And furthermore, if a patient calls a pharmaceutical company and says I am a patient, can you give me information about XYZ, the response will almost uniformly be, I cannot answer your question. You will have to go speak with your doctor.

Ms. MATSUI. Thank you very much. Ms. Charo, I know you have concerns about the legislation that we are discussing today. Are there ways that we can refine the legislation to reach our shared goal of promoting public safety by increasing patient access to safe and effective drugs? I think there is information out there and you know, we are in a time now where there is much more research and innovation and I would hate to just have a hard and fast rule regarding this.

Ms. CHARO. Thank you. I completely agree with you that there are other avenues that need to be explored. For one thing, it may make sense to try to distinguish those areas where off-label use really is a necessary and important part of medical care as we just heard in the area of cancer, and some other areas there it really is not as prevalent and is not as needed. And I would suggest that pediatrics may be another good example.

And the Congress has made great strides in trying to create new systems for both incentives and even possibly rewards for continuing the necessary research to find what really is safe and effective, for example, in the pediatric population. Working on making sure that there is a proper incentive and reward to fill in the gaps in those areas would be a good step forward and might accomplish many of these goals without some of the risks that are intended upon some of the ambiguities and what constitutes promotional marketing or what constitutes accurate information.

Ms. MATSUI. Thank you. I have run out of time. I yield back.

Mr. BURGESS. The Chair thanks the gentlelady. The gentlelady yields back. The Chair recognizes the gentleman from Indiana, Dr. Bucshon, for 5 minutes for questions, please.

Mr. BUCSHON. Thank you, Mr. Chairman. I was a practicing cardiothoracic surgeon prior to coming to Congress and I just have

a comment, not a question, but the medical community is relatively small and I think Dr. Van Hare said there is 300 pediatric cardiologists. There is about 4,500 to 5,000 cardiac surgeons. Information travels quickly. Physicians are always looking for better ways or effective ways to treat their patients whether it is on label or off-label and information passes quickly.

Frustration with labeling can be really high amongst different physician communities because of the delay in updating what may or may not be FDA-approved. Patients are desperate and are getting information potentially from incorrect sources including the internet as has been pointed out and so I would suggest that we definitely need reform so that patients have the opportunity to get more accurate information.

With that, I am going to yield the remainder of my time to Mr. Griffith.

Mr. GRIFFITH. Thank you very much. I appreciate it greatly. Let me first say that I appreciate everybody being here today and appreciate all of your testimony. I am open to continue to work on the language to make sure that we get it right. So that is something that I would invite you all, if you have issues with the language that we currently have, please get those suggestions to us because we want to try to do this in the best way that we can. We do believe that we need to do something on a legislative side.

Also, Mr. Chairman, I have some letters in support of the bill and a draft language, and, if I could have unanimous consent to enter those into the record, I would appreciate it.

Mr. BURGESS. If the gentleman will share those with us, I will seek unanimous consent in a moment.

Mr. GRIFFITH. I also want to make sure that we are all working on the language that we currently have. And so what the bill says is, when we are talking about communication, if you look on page 2 it says, "(a) the communication is not advertising or otherwise promotional in nature; (b) the communication is supported by competent and reliable scientific evidence." And then (c) and this was to address some of the concerns that have been raised here today, we put this language in: "The communication clearly discloses appropriate contextual information about the data presented including information about limitations." And I probably should put numbers in front of these. "(1) Limitations of the data; (2) the scientific and analytical methodologies used; and (3)"—and I think very importantly—"any contradictory data or information known to the manufacturer or sponsor."

We are never going to solve all of the problems if somebody is not doing what they are supposed to do, but our intent is to try to make sure that both sides are presented. I think somebody mentioned that earlier in their testimony, that both sides are presented and that the negative evidence is out there as well.

And then we talk about situations related to the rare diseases. Cancer has been mentioned today and the children because one of the problems you have in those situations and Dr. Van Hare, you touched on this is that there may not be a sufficient number of patients to actually warrant doing a clinical study. Nothing compared to what you deal with your families Dr. Van Hare, but my son who is now 11 had $\frac{2}{3}$ of his body covered with eczema when he was

about 3 months old. I kept telling my wife because of the history in the family we have allergy problems, honey. We got him to an allergist. Between the cream that worked for me that my pharmacist knew, between the steroid creams, between the antihistamines that they gave him, we were able to control that situation. We still have issues there. But for a child under the age of 2, there were no—some of that might have been on-label, but most of that treatment was off-label, so I appreciated Ms. Charo saying that we ought to take a look at that, because I think those are the two hot-button areas. But that doesn't mean we should exclude others.

I was very curious, too, about this whole agent concept that is going on where you can't go and tell the 300 other doctors, Dr. Van Hare. Could you speak on that briefly, and I have only got a minute left of this time period.

Dr. VAN HARE. Yes. It has to do with how CME or Continuing Medical Education is defined. CME is actually a safe harbor. If I am speaking at a conference that is sponsored by an accredited CME provider, like the Heart Rhythm Society or the American College of Cardiology or some other group, I can say whatever I want and I can talk about off-label indications as much as I want. If I am actually speaking at a conference that is actually sponsored by the pharmaceutical company or the manufacturer, then I basically am an agent, or considered an agent.

Mr. GRIFFITH. So if on the podium somebody asks you about a catheter to be used in a child that might be off-label, you could then be deemed and the company could be deemed that you are their agent and then be in trouble under the current rules of the FDA. Is that correct?

Dr. VAN HARE. That is my understanding.

Mr. GRIFFITH. That is my understanding also. All right, Ms. Klasmeier, my friend and colleague from New Jersey, Mr. Lance, did a great job of going through the intellectual. Let us translate that into human regular English. That means that if you bring that example to the courts, FDA is most likely going to lose, wouldn't you agree?

Ms. KLASMEIER. I would agree and I would go one further. FDA did lose that case. That was the Washington Legal Foundation decision in 1998 and the upshot of that is that the court found it unconstitutional for the Government to purport to restrict the identity of the speakers that could participate in those kinds of continuing education events that Dr. Van Hare described.

Mr. GRIFFITH. Thank you very much. I yield back to my colleague. Thank you.

Mr. BUCSHON. I yield back.

Mr. BURGESS. The gentleman had a unanimous consent request and I sought counsel from the other side of the dais, so without objection, so ordered if that unanimous consent request still stands. [The information appears at the conclusion of the hearing.]

Mr. GRIFFITH. It does, and I apologize. I just saw my time taken away.

Mr. BURGESS. Very well. The Chair recognizes the gentlelady from Florida, Ms. Castor, for 5 minutes for questions.

Ms. CASTOR. Well, thank you very much, Mr. Chairman, for calling this hearing. I think allowing drug companies and manufactur-

ers to market their drugs and devices for unapproved uses would be very dangerous for American families, American consumers. It would reduce the incentive for them to go through FDA's approval process and reduce the incentive to go through clinical trials that really just test whether or not a product is safe and it is effective. FDA's approval process right now is the gold standard for safety and efficacy.

The FDA Commissioner, Dr. Gottlieb, has said the most important incentive to developing useful information remains the ability for companies to market drugs based on what can be proven scientifically. Now this is not a hard and fast rule because I have learned today and reviewing your testimony, there are safe harbors, but nevertheless, Professor Charo, some contend that we must revisit this regulation of off-label promotion because the trend in the courts is that restrictions on off-label promotion run afoul of the First Amendment. I think this is a stretch. Does the First Amendment limit FDA's responsibility for scientific review? Does it limit FDA from restricting promotion of unapproved uses? If not, what avenues do medical product manufacturers have to communicate about such uses?

Ms. CHARO. Well, we have seen some cases that have touched on these things from the fringes, but you don't actually get cases that touch on it directly. For example, in one case that is frequently cited for the suggestion that the Constitution prevents the FDA from restricting truthful speech, at issue at the time was not truthful speech, but simply off-label speech and the FDA premised its entire case on the fact that the speaker had been discussing an off-label use and never really talked to the issue about whether or not the speaker's comments had been true.

The problem here has simply been that it is really and I hope that Mr. Griffith's staff is still around for this, the problem is that no company is going to have all the information about all the studies that are being done at that time including those that have negative results because of various rules about confidentiality of information. The FDA may be in possession of all the information, but not necessarily every company. So even with the best of intentions to be conveying what they believe to be truthful and contextualized information, there is the risk that that actually is missing large areas of data that would suggest that the studies they are discussing are not, in fact, going to be indicative of a truly safe and effective drug at the end of the day. This is why there really is a substantial public interest which is one of the key elements in the restriction of speech to the current system.

And the alternatives that have been presented, unfortunately, I believe offer risks to public health that dwarf their benefits which is why the second rung, the second prong of these tests which have to do with whether or not the Government can find an alternative way of achieving its goals I think show that really the current system is probably the best way, tweaking, yes, but the removal of many of these restrictions, I don't believe is necessary in order to meet the Constitution test.

Ms. CASTOR. And there seems to be debate on whether the Griffith proposal would restrict scientific exchange under the safe harbor. What is your view of this and the Griffith discussion draft?

Ms. CHARO. You know, I think that the text does attempt does attempt to isolate what is nonpromotional and protect that while continuing the prohibit promotional language. I think that the difficulty here is that the very notion of what is promotional is actually somewhat ambiguous. We now know, for example, that it is possible to tweak how various results come up on the internet, whether or not it is the first, second, or third thing you see on the page. If there is a tweaking algorithm, does that constitute promotional if all it does is raise your particular data to the front of the page? These are the kinds of subtle questions that can both make the language ambiguous despite our efforts and also from my perspective, suggest that it is better to have the flexible tools of guidances that can be negotiated over time with the constantly changing nature of communication rather than the somewhat more rigid tools of regulation and legislation, let alone having courts do it 17 years after the fact and leave everybody uncertain for that long period in between.

Ms. CASTOR. Dr. Kesselheim, do you have a comment on this topic as well?

Dr. KESSELHEIM. I mean I also agree that the way that this discussion draft is written provides substantial leeway for companies to interpret these various provisions in ways that are favorable to their particular advertising strategy.

Ms. CASTOR. And at the cost to public safety.

Dr. KESSELHEIM. And at the cost to public safety.

Ms. CASTOR. Thank you. I yield back. I am out of time.

Mr. BURGESS. The gentleman yields back. The Chair thanks the gentlelady. The Chair recognizes the gentleman from Georgia, Mr. Carter, 5 minutes for questions, please.

Mr. CARTER. Thank you, Mr. Chairman. And thank all of you for being here. Certainly, an important subject.

Dr. Khachatourian, you are a pharmacist, as am I. And I can tell you that after 30 years of practicing pharmacy, certainly side effects are—we call them side effects. And you know, it has always been interesting to me why we call them side effects because essentially they are effects of the drug, but they are not what we want it to do, so we kind of label them as side effects.

I noticed in your statement, in your testimony, in your written testimony that you feel like the Pharmaceutical Information Exchange would be helpful and useful and there is some debate on whether it should be evidenced based or whether it should be information based. And I noticed that you said that it should be based on information only, well, not only, but basically. Can you kind of elaborate on that?

Ms. KHACHATOURIAN. Absolutely, thank you. So when we think about evidence, there are established criteria for evidence as far as what constitutes a clinical trial and the acceptable level of evidence for FDA approval. When I talk about information, information may include financial models, may include other information that does not quite meet the level of evidence that one might traditionally think. So when we talk about information, if I am able to discuss with my clinical colleagues at a manufacturer what models might be available, what sub-populations were studied and what level of

information might be available that can help me to make more effective decisions, that is what I mean by information.

And again, I will reference the multi-stakeholder forum where we discuss developing criteria that will set the foundation for what that information might entail and what level of quality of information could be deemed acceptable.

Mr. CARTER. You also mentioned in your testimony that a very proactive pharmaceutical information exchange would lead cost savings. It could lead to cost savings for patients. So in that respect, how can we assure that the cost savings are going to be passed on to the patients if we don't have transparency within the prescription benefit managers and the other middle men that are included so often in these scenarios?

Ms. KHACHATOURIAN. Sure. While cost is an aspect of evolving and emerging therapies and treatments that are coming, cost is an aspect that needs to be discussed. However, with the exchange of information it makes us more effective in the use of the funds that we have available to make benefit decisions. So when we are structuring a benefit based on value, that is what value will be conveyed to both us as the payer as well as the patient. So ultimately from a cost discussion, that is, in turn, outside of the transparency which is a little bit of a different discussion.

Mr. CARTER. I am not sure I understand how it can be a little bit of a different discussion. Because I believe truly that it can have cost savings to the patient if we have transparency within the system and I don't see how it can be if we don't have transparency.

Ms. KHACHATOURIAN. So I absolutely acknowledge transparency is an important factor. However, the information exchange between a payer, as well as the manufacturer, will help us to make better decisions and with a limited pool of money that we are able to allocate to benefit design. We try to make the most cost-effective decisions on behalf of those patients that we serve, so in turn, the cost savings are passed to the patient as the ultimate user of our benefit design.

Mr. CARTER. OK. I will move on. Dr. Van Hare—and thank you very much for being here, Dr. Khachatourian.

Dr. Van Hare, I have seen in my practice over the years, particularly with prescription drugs, a lot of off-label uses, if you will, in pediatric patients. And I just want to get your feeling on the value of that? Because I have seen it first hand that it has been very valuable.

Dr. VAN HARE. Yes, well, so I would say it is essential, in fact, for most of what we do, particularly in the pediatric cardiology area. But I mean I do think we have reservations about it. When people make decisions based on information they get from like one other colleague who used it once on some patient, that is very, very sort of limited. But I would say that certainly we have to do it. We have no choice but to do off-label prescribing in a lot of situations. And we would prefer to have the best possible information.

We also use what is known about the use of these medications in other age groups, particularly adults, or other particular conditions and basically extend to these particular populations. That may or may not be valid as some other members of the panel here

have talked about. But absent better data, it is all we actually have.

Mr. CARTER. Great. Thank you all very much for your participation here today. A very important subject I can tell you. Many years of practice in pharmacy, we have used many drugs that were not indicated or at least not approved for certain therapies that have been very, very beneficial to patients.

Thank you, Mr. Chairman. I yield back.

Mr. BURGESS. The Chair thanks the gentleman, the gentleman yields back. The chair recognizes the gentlelady from California, Ms. Eshoo, 5 minutes for questions, please.

Ms. ESHOO. Thank you, Mr. Chairman. And thank you to all of the witnesses. I also want to thank our colleagues who are offering the drafts and to Mr. Griffith, I especially appreciate your openness to suggestions and I think that that is very important.

Over all the years I have been in Congress, this is my 25th year, and have worked with medical device manufacturers, worked with the biotechnology industry, done legislation that has reformed how medical devices are approved, passed legislation signed into law, but I can't remember which President relative to pediatric medications, and improved that system for children. This issue, the issues that are being discussed here today, no one has ever raised with me. So this is the first time I am hearing about it. But it is good. It is a discussion, but it still says something to me that no one has contacted me about this. So I don't think it is exactly a burning issue.

Number two, it is my understanding that what is being offered by our two colleagues today were supposed to be a part of the overall approval for the FDA, but were pulled because they were controversial. I can hear today where the controversy is coming from. That is legitimate and I am glad that it wasn't in the larger bill, because they really didn't belong there. This cake has not been baked yet.

Now it is my understanding that in one of the discussion drafts, that there is no clear list of what qualifies as scientific information. Now that is foundational to me, scientific information. Not who is gabbing and saying what from a given industry. That is always interesting and those discussions take place. But we are dealing with over 200 million people in our country and these words are going to walk into their life. This is a huge responsibility. They don't know that we are here today. They don't know any of our names, but we have the public interest in the safety and the efficacy of what takes place on their behalf.

To Ms. House, I am not sure, are you in favor of the two discussion drafts? Yes or no?

Ms. HOUSE. We have not taken a formal position on either.

Ms. ESHOO. That is fine.

Ms. HOUSE. Neither of them are perfect.

Ms. ESHOO. Yes, well, but I couldn't tell from your testimony whether you were for or against or where you were.

Ms. Charo, thank you for your testimony. I think that you have set down the importance of where the information comes from and that it can't be haphazard. There has to be a final kind of resting

place that has all of the information for people in our country that can be used.

I don't think anyone has really made the case here to take it outside of the FDA. Maybe I am missing something, but I haven't heard that.

To Ms. Khachatourian—I love the I-A 09N; I share either your husband's heritage or yours—when you spoke about hep C, how many patients were excluded from treatment?

Ms. KHACHATOURIAN. So while I can't speak for all payers and all—

Ms. ESHOO. No, but you used that as an example, hep C. So we know, it is a company I am very familiar with in my district. I have worked with them. They have presented a cure which we are not accustomed to. It is expensive. But who was left out, according to your testimony?

Ms. KHACHATOURIAN. Sure. So in the initial approval, we approved treatments according to the label. So for the first time in hepatitis C, we saw the criteria, the approval criteria change multiple times. So initially it excluded patients that might have cirrhosis. It initially excluded patients that according to the FDA label—

Ms. ESHOO. How do these drafts fix that?

Ms. KHACHATOURIAN. So with the drafts, we could understand that there would be evidence published that would add additional clinical evidence to indicate effectiveness of treatment in those sub-populations although at the time of the initial approval, that evidence was not available for decision making.

So in my medical space—

Ms. ESHOO. You are saying people were excluded, but you don't know how many?

Ms. KHACHATOURIAN. I can't speak to the exact number globally. However, within our population, Medicare is who defines our coverage criteria. So when we submit our criteria to CMS for approval, it has to be according to the Part D coverage, what is listed in the FDA-approved label. So we cannot cover off-label unless it is within the oncology space. When we are talking about a Part D indication.

Ms. ESHOO. I still don't know who has been injured in this according to your testimony. That is why I am asking you, and I still don't know. But I appreciate your trying.

Thank you, Mr. Chairman.

Ms. KHACHATOURIAN. If we expand the discussion to commercial payer outside of Part D, the additional patients that were denied treatment.

Ms. ESHOO. But you don't know how many.

Ms. KHACHATOURIAN. I don't coverage commercial insurance, however, that is something I would be happy to look into for you.

Ms. ESHOO. Thank you.

Mr. BURGESS. The gentlelady yields back. The Chair thanks the gentleman. The Chair recognizes the gentleman from Virginia, Mr. Griffith, 5 minutes for questions, please.

Mr. GRIFFITH. Thank you very much. I appreciate it. Ms. Klasmeier, we have had some discussions and I know this is not the Judiciary Committee, but this is where the law touches everything. And so as we consider legislation in this area, just so the

committee knows as a whole and that I am better educated, what points should we be taking away from the various judicial cases in considering First Amendment challenges to the FDA's regulations? And what should we be looking out for? So that is Part A and Part B. What should we be looking out for to make sure that we get it right and that we do it where it is constitutional as we draft this?

Ms. KLASMEIER. Thank you very much for the question, Congressman. I think a very important take away from the case law is the need for clarity and that point arises out of the intersection of the Fifth Amendment case law and the First Amendment case law. I think there is a lot of discussion about the First Amendment, but the due process laws requires clarity and precision, requires rules that give regulated entities clear notice on an a priori basis of what conduct is prohibited versus permitted.

Mr. GRIFFITH. And let me, I don't want to cut the rest of the answer off, but let me interrupt up there because that is one of my pet peeves. So many times people think that means we have to define every word in the bill, but if there is no definition in the bill, then the courts use the normal usage of the English language or if it is a term of art, the term of art in this case from the medical community. Is that not correct?

Ms. KLASMEIER. It is absolutely correct, sir. And just to augment your observation, there was a conversation earlier this morning about the definition of claim and promotion and where do we draw the line. And I understand why there may be some misunderstanding around that, but I have to say as a practitioner in this area—and I also have to say I suffer from a little bit of an existential crisis because the news that this is not a hot-button issue or something that needs to be resolved makes me question what I have spent the last 20 years of my life doing. But that is an aside.

Mr. GRIFFITH. No worry, her phones will be lit up before the day is done, I am sure.

Ms. KHACHATOURIAN. But there is among those of us who practice in this area day in and day out a very well-understood line between promotional speech and nonpromotional speech. So I think the legislative measures that we have been talking about this morning would just under foundational interpretive principles be examined against those background legal norms. So there is a very rich body of administrative precedent from FDA in addition to case law and the statutory foundation of the measures that you are talking about. We know what these words mean. So I agree to the extent that you are saying we ought not to feel overly anxious about those two or three words. I think folks who are battle tested in this area know the difference between promotional speech and nonpromotional speech and can advise clients accordingly.

Mr. GRIFFITH. And I kind of got you off track there for a second. You were talking about the First and the Fifth. I am going to let you go back to is there anything else on that you wanted to touch base on that I distracted—

Ms. KHACHATOURIAN. Many things, but I will try to limit it to a big-ticket item, which is it is increasingly obvious from the case law, which goes back to at least to 1976, that it is very hard for the Government to defend any speech regulation that affects accurate communication regarding lawful activity. I think we tend to

get hung up on the kind of Central Hudson test and prongs and that sort of thing. But just to sort of bring it down to its essence, if the Government wants to restrain accurate speech about conduct that is permitted—and off-label use is not only permitted in almost all cases, it is by Federal law, it is also the standard of care in many instances—it has really got an uphill battle.

I think there is probably a way for all of these very challenging and complex policy considerations to be balanced in a smart way that takes account of the First Amendment backdrop, and I think the measures that we are talking about today have done an admirable job of strengthening that balance. But there is a little bit of a thumb on the scale, if you like, as a result of years and years of case law going back to at least 1976 against anything that would purport to prohibit accurate speech about lawful activity.

Mr. GRIFFITH. And while I wasn't as concerned about the freedom of speech, per se, although it is very important to me, when I put in that clause that they have to put in the contradictory information, as well, and the contextual information, that actually shores that up from a free speech standpoint as well, because we are saying you have to present—if you are going to present—you have to present both sides of the data. Isn't that accurate?

Ms. KHACHATOURIAN. Absolutely accurate, yes, sir.

Mr. GRIFFITH. I appreciate that. And it does make me worry and I know it is not their field of expertise either, but you indicated there was a late '90s case that clarified some of this. I think the bill clarifies it more, but I am just curious why the FDA keeps going down this pathway when they have lost a number of cases over the years, if not in this circle of the three-ring circus, in another circle of that same circus under the same tent.

Ms. KHACHATOURIAN. Yes, well, it is concerning because you have not only the cases that we have been talking about here, Caronia and Amarin and Pacira, but also on the dietary supplement side of the house, a great many cases from the DC Circuit, a lot of other sources of precedent that draw into question the constitutionality of the current scheme. That said, I think there are a lot of undeveloped arguments that we have been, in industry, waiting with bated breath for FDA to articulate and there was a memorandum that FDA lodged in one of its administrative dockets in January, right before the inauguration that purported to explain for all the world to see how the agency thought through these constitutional issues and it was a little more than a defense of the status quo.

I think there is a lot of room for optimism in the coming months, particularly with the involvement of this subcommittee and the Congress, generally, that FDA will do a better job of explaining and including stakeholders in a conversation about the constitutionality and constitutional issues associated with this current regulatory scheme.

Mr. GRIFFITH. I appreciate it and yield back. Thank you, Mr. Chairman.

Mr. BURGESS. The Chair thanks the gentleman. The Chair thanks Ms. Khachatourian for her optimism. We always welcome optimism on this subcommittee.

The Chair now recognizes the gentleman from Maryland, Mr. Sarbanes, 5 minutes for questions.

Mr. SARBANES. Thank you, Mr. Chairman. I want to thank the panel. This is a really complicated issue, I am finding. I sat here through the entire testimony. And certainly the ability and the internet is kind of at the center of this now for people to get hold of information about beneficial off-label use of drugs and medical devices much more readily than obviously they ever could before, is creating some pressure to figure out a way to make that opportunity more available to people. The fast distribution of information can also allow for the fast distribution of bad information and lead to poor decision making. But I understand that Congressmen Griffith, Guthrie, and others are trying to respond to pressure and often it comes from patients that are seeking a solution.

What I am concerned about is that you could solve the way they are proposing for this pressure, or you could solve perhaps by building more capacity inside the FDA. So what I am interested in hearing about, I don't want us to take a shortcut. I don't want the reason we are reaching for the proposed solution here to be that we have overlooked the opportunity to build more capacity in FDA as a way of solving for this, and perhaps solving for in a way that protects public safety better than taking the alternative route.

So I wonder, Ms. Charo, maybe you could begin here. Speak to that issue. How do we explore fully the opportunity to build capacity in FDA to respond to the pressure we are talking about? Can that be done? If so, what are the ways in which it can be done, et cetera?

Ms. CHARO. Well, first, I am going to second what has been said by others here which is that FDA, just in terms of sure personnel, would certainly benefit from having more people able to act on data as it is coming in and everything would move more rapidly with no question. But we shouldn't restrict ourselves only to FDA. I mean one of the things we have been struggling with here is that there are areas in which the incentive systems that currently exist are inadequate for driving the research that we all agree would be ideal to figure out what really works and what does not. Pediatrics, rare diseases are two very good examples.

Now we have some new tools. Congress have given things like priority reviews and extended patent periods as incentives, but we have yet to completely explore the full range of tools. Antibiotics is another example where the Infectious Disease Society of America has been pointing out for years we could use rewards, milestone rewards. We have not talked about NIHI funding for direction of studies that would look at things like off-label uses that are hinted at already and that need to be confirmed.

In other words, we need not restrict ourselves to only one tool which is to pull the industry slowly to do the research under the threat of not being able to market. But we could bring to bear a combination of tools to get the information developed more rapidly. And ideally, then everybody would benefit because we would have a wider range of applications, but we would have more confidence that they have been tested in a way that is comprehensive and objective and has been vetted by independent eyes.

Mr. SARBANES. I appreciate that. I mean, I worry a little bit that I don't completely trust the industries we are talking about here to restrain themselves if they get—if there is an avenue for aggressively pursuing a particular product's appeal out there in ways that may compromise public safety, and I worry about a bunch of camels starting to get their noses under the tent. So I understand the desire to try to accommodate people's interest in pursuing this, but if there are other ways we can respond to that, without sacrificing some of these concerns about public safety, then I think that we ought to pursue those and explore some of the additional tools that you have suggested, perhaps. With that, I yield back. Thank you.

Mr. BURGESS. The gentleman yields back. The Chair thanks the gentleman. The Chair recognizes the gentleman from Florida, Mr. Bilirakis, 5 minutes for questions.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I thank the panel as well. I have a question for Ms. House. Again, thank you for your testimony. Throughout my time on the Energy and Commerce Committee, I have been involved with the rare disease community. There are about 30 million Americans—and there are 7,000 rare diseases—30 million Americans have a rare disease, which includes pediatric cancers. And I understand there are about 500 FDA-approved treatments. Correct me if I am wrong.

Do you think that many of these 30 million Americans are taking medications off-label? For Ms. House, please.

Ms. HOUSE. Yes. Yes, I do. I do. In my written comments, I have referenced in particular lupus, and if you look at the FDA site right now, there are only four drugs that are approved for lupus. And the approvals of those go back into the mid-1900s. So when you look at the drugs, aspirin was approved first in 1948, followed by steroids, and there was no drug listed. There was an antimalarial that was approved in 1955. And finally, a new drug approved in 2011. So if you are a patient living with lupus, you are likely not getting aspirin as a therapeutic option for your particular disease. And certainly when you look at cancer, there is a reason why there is such a high rate of pediatrics in cancer clinical trials, and it is because they don't have a lot of other options available to them.

Mr. BILIRAKIS. Thank you, so there are other examples out there. So a large percentage of the 30 million are taking medication off-label.

Ms. HOUSE. Arthritis is another good sample. If you look at the label of methotrexate, for example, you will see that the label doesn't reflect the broad use of that particular product and you can probably speak to that better than I could.

Mr. BILIRAKIS. Thank you. I am here with a young Floridian from the Miami area who told me about how she came down with ITP, a condition where her body destroyed her platelets. And I have conversed with her over a long period of time on these particular issues. I have sponsored the Open Act and we are working together.

She had to become an expert. She became an expert on ITP, and she really became her own doctor and found a treatment, really extraordinary. She was able to find a drug that could treat her condition. The drug was FDA-approved for non-Hodgkin's lymphoma and rheumatoid arthritis, but not for ITP.

After a long conversation with her physician, we were able to pursue that course, the off-label treatment, and it was very successful. She comes to DC on a regular basis as an advocate for cures and treatments for rare diseases.

Ms. HOUSE, does it make sense to withhold information from physicians and not share truthful medical information that could save a person's life? And who should be in charge of a patient's treatment? The patient working with her physician or again, a bureaucrat? If you could answer that question, I would appreciate that.

Ms. HOUSE. Well, you know, we have spent 35 years trying to assist patients to become equal participants and empower participants in their care, so I am going to answer that as the patient needs to be quarterback of their care, working with their particular physician.

I will say that it is incredibly important though that the information that is provided, both to patients and to physicians, is fair balanced. I worked in the pharmaceutical industry for a period of time, so I also understand the bright white lines between what is promotional and what is nonpromotional and we are not talking about shipping patients or physicians glossy pieces of information on off-label uses or other additional information, but we have to provide for them and whether that is, I do agree that there are alternative solutions, whether it is through the FDA, whether it is through a professional society, whether it is through a third party peer reviewed entity, we have to get to a point where we are providing that data set to people who are making decisions, including patients who are making more and more of their care decisions as you have referenced.

Mr. BILIRAKIS. Thank you. Agreed. Dr. Van Hare, in your practice, you deal with children and adults who suffer from a heart condition such as the congenital heart and some are congenital heart in nature. I sponsored a bill to reauthorize a congenital heart program and it went through this committee and hopefully on the floor as soon as possible.

If you have a child who comes to the hospital with a heart condition, you might need to do a surgical procedure. How common is it for medical devices to be approved for use in children?

Mr. BILIRAKIS. Well, as I understand, most medical devices, at least that I use in the cardiology sphere are not specific to children or adults. They are more specific to actual specific arrhythmias. And as I talked about in my oral testimony, a lot of what we take care of, the devices, in fact, are not labeled for those particular sort of conditions.

I will say that you sort of raise the issue of surgery for congenital heart disease. We often think about surgery as basically correcting a problem. But those patients need to have a cardiologist for the rest of their life and one of the biggest problems if they develop heart rhythm issues and those heart rhythm issues are often very, very difficult to take care of and so we are reaching for whatever we can find to treat those things most effectively. And we use technology and we use devices that have been approved for other indications for this particular situation.

I just want to emphasize that we keep talking about pediatrics as sort of being an important issue and I am a proud pediatrician

and I believe that. But I think pediatrics is a special case of a larger issue which is there are a lot of patients that devices and drugs have been developed for other indications. We have to find a way to take care of our patients. I think pediatric diseases, but also rare diseases, and anything that is kind of on a cutting edge of what we are doing medically to treat things are going to fall into this discussion.

Mr. BILIRAKIS. Thank you very much. I yield back, Mr. Chairman.

Mr. BURGESS. The Chair thanks the gentleman. The gentleman yields back. The Chair recognizes the gentleman from New York, Mr. Engel, 5 minutes for questions, please.

Mr. ENGEL. Thank you very much, Mr. Chairman. I have long been an advocate for those suffering from rare diseases. I was an author of the ALS Registry Act and the two most recent Muscular Dystrophy Care Act reauthorizations and I know how much relief and encouragement new therapies can bring to rare disease patients. And I think I speak for everyone on this subcommittee when I say that all of us want to do what we can to bring effective and potentially life-saving treatments to patients as quickly as possible, but it is absolutely critical that we ensure our actions do not compromise patient safety.

Efficiency is a worthwhile goal that we all share, but as we strive to hasten the delivery of new treatments, safety and effectiveness must always be paramount and that is why this hearing is so important. Any action by this committee needs to take into account the input of expert witnesses who can speak to the potential implications of our actions. And that is what we have, Mr. Chairman, in our panel. And so I want to thank today's witnesses for being here and sharing your insights.

Let me start with Ms. Charo. During your testimony, you noted that "approval of a drug for labeled"—I am quoting you—"indication does not mean it will be safe and effective for off-label uses." And that "additional studies are needed to explore them."

Now it would seem to me that if a manufacturer wished to communicate about an off-label use for a product that manufacturer must already have reason to believe that this product is safe and effective for the given off-label use. So if there is already evidence supporting an off-label use, can you explain why additional studies would be necessary?

Ms. CHARO. Of course. And I think other people on this panel are even more expert than I in research trial design, but the reality is that evidence comes in many forms and often it is based on small numbers of people with very homogenous kinds of situations. But in the real world, you need larger numbers of people with a wider variety of background conditions and complexities in order to detect both the areas in which it will or will not be effective. It might depend upon co-morbidity, and also to detect some of the less common kinds of side effects or adverse events.

And those things are relevant to deciding whether or not the benefit that some people get will be sufficient to outweigh the kinds of risks or failures to work for other people.

So initial evidence often can look extremely promising. Pre-clinical evidence, particularly we have cured cancer in mice count-

less times, but also early human evidence is often very, very promising and then when we move into larger trials with more complicated and more diverse populations we discover that, unfortunately, it was misleading. And it is just a matter of basic statistics as well as medicine. That is why there is such an emphasis on properly controlled trials of sufficient size and statistical power and the ability, too, to look at the possibility of inherent biases and how you structure the trials. It is very easy to structure trials in a way that subtly lead to one conclusion or another without even intending to do so. That is the value of the independent expert eyes that the agency brings.

Mr. ENGEL. Thank you very much. Dr. Kesselheim, you also touched on the need for additional studies in your testimony. So I would like to ask you the same question. If there is already evidence supporting an off-label use, can you explain why additional studies would be necessary?

Dr. KESSELHEIM. Sure. I mean if there is evidence supporting an off-label use and there are certainly plenty of ways that that evidence can already be communicated under the current rules. I think the rules are fairly clear about what types of communications are, where there are opportunities to communicate that information. And if there are additional studies and again, I think the importance is what is the nature of that evidence. How is that evidence defined? What are the statistical methods that were used in testing? How is the population defined? And these are details that, you know, average physicians don't know a lot, don't have a lot of training in and don't know a lot about it and these are the details that the FDA has expertise in. And so if there are nuances that might not be caught in initial examination of the information, additional studies that are necessary, then the numerous dozens of experts at the FDA with training in various different fields can identify that and pick up on that and determine whether or not what might initially be seen in the data, turns out to be legitimate.

Mr. ENGEL. Thank you. Ms. Charo, I have one final question for you. It is my understanding that in January the FDA released draft guidance regarding which manufacturer communications are consistent with the FDA required labeling in which are not. And I understand also that this guidance has not yet been finalized.

So do you feel that draft guidance strikes the right balance between enabling potentially helpful communications to take place and protecting patient safety and why shouldn't we legislate in this space to provide even greater clarity for manufacturers?

Ms. CHARO. I do think the FDA is moving in the right direction. I agree that draft guidances would be better off if they were finalized guidances, although it is worth noting that a tremendous amount is already done through draft guidances at the FDA without any Fifth Amendment due process questions being raised about it.

The thing that I think is most important about what the FDA has been doing is its insistence that actual knowledge about how your product is being used can be in some instances considered to be evidence that you actually intended for the product to be used that way. I think a lot of the debate has been around that phenomenon. But we have seen that phenomenon in other contexts.

We have seen it in areas having to do with constructive knowledge in tort law where if you know something is about to happen and you actually go ahead and do all the things that are necessary for it to come about, you are actually going to be considered to have intended that to happen in many cases.

On the other hand, we have seen in the area of gun law, a lot of resistance to the idea that actual knowledge constitute intent. I do think that is an area where we have to have some more discussion to clarify, but I also think that it is risky to simply allow for an expansion of communication while simultaneously saying but now that I have communicated more, the fact that I know that it is having an effect doesn't mean that I intended that particular outcome. I think to have both of those things at once I think is particularly risky. Choosing one or the other at least would be the right direction.

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

Mr. BURGESS. The gentleman yields back. The Chair thanks the gentleman. Does the gentleman from Texas have a unanimous consent request?

Mr. GREEN. Yes, Mr. Chairman, I have a consent request.

Mr. BURGESS. I will yield for a unanimous consent request.

Mr. GREEN. I move that we have statements in the record from the American Health Insurance Plans, the Campaign for Sustainable Drug Pricing, and also Public Citizen Action be placed into the record.

Mr. BURGESS. Without objection, so ordered. Seeing no other Members wishing to ask questions, I once again want to thank our witnesses for being here today.

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

Mr. BURGESS. Pursuant to committee rules, I remind Members they have 10 business days to submit additional questions for the record. I ask the witnesses to submit their responses within 10 business days upon receipt of those questions. And without objection, the subcommittee stands adjourned.

[Whereupon, at 12:37 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

1 **SEC. ____ . FACILITATING EXCHANGE OF INFORMATION**2 **PRIOR TO APPROVAL.**

3 Section 502(a) of the Federal Food, Drug, and Cos-
4 metic Act (21 U.S.C. 352(a)) is amended—

5 (1) in paragraph (1)—

6 (A) by striking “formulary committee” and
7 inserting “formulary or technology review com-
8 mittee”;

9 (B) by striking “drugs for coverage” and
10 inserting “drugs or devices for coverage”;

11 (C) by striking “approved under section
12 505 or under section 351(a) of the Public
13 Health Service Act for such drug” and insert-
14 ing “approved, cleared, or licensed pursuant to
15 section 505, 510(k), 513, or 515 of this Act or
16 pursuant to section 351 of the Public Health
17 Service Act for such drug or device”;

18 (D) by striking “approved for the drug
19 under section 505 or under section 351 of the
20 Public Health Service Act” and inserting “ap-
21 proved for the drug or device pursuant to sec-
22 tion 505, 510(k), 513, or 515 of this Act or
23 pursuant to section 351 of the Public Health
24 Service Act”; and

1 (E) by striking “The requirements set
2 forth in section 505(a) or in subsections (a) and
3 (k) of section 351 of the Public Health Service
4 Act” and inserting “The requirements set forth
5 in section 505(a), 510(k), 513, or 515 of this
6 Act or section 351 of the Public Health Service
7 Act”;
8 (2) by redesignating subparagraph (2) as sub-
9 paragraph (3);
10 (3) by inserting after subparagraph (1) the fol-
11 lowing:
12 “(2)(A) Health care economic information or sci-
13 entific information provided to a payor, formulary or tech-
14 nology review committee, or other similar entity with
15 knowledge and expertise in the area of health care eco-
16 nomic analysis carrying out its responsibilities for the se-
17 lection of drugs or devices for coverage, reimbursement,
18 or other population-based health care management, shall
19 not be considered false or misleading or any other form
20 of misbranding under this paragraph, or a violation of sec-
21 tion 505, 510(k), 513, or 515 of this Act or section 351
22 of the Public Health Service Act, if it is based on com-
23 petent and reliable scientific evidence and relates to an
24 investigational use of a drug or device.

1 “(B) In order for information relating to an inves-
2 tigational use of an approved, cleared, or licensed drug
3 or device to be provided pursuant to this subparagraph—

4 “(i) the study or studies the sponsor anticipates
5 could be sufficient to support the approval, clear-
6 ance, or licensing of such use must have been con-
7 ducted;

8 “(ii) the sponsor must intend that a supple-
9 mental application will be submitted to the Secretary
10 for approval, clearance, or licensing of the use; and

11 “(iii) the information must include, where appli-
12 cable, a conspicuous and prominent statement de-
13 scribing any material differences between the infor-
14 mation provided and the labeling approved pursuant
15 to section 505, 510(k), 513, or 515 of this Act or
16 pursuant to section 351 of the Public Health Service
17 Act.

18 “(C) For purposes of this subparagraph, scientific in-
19 formation includes clinical and pre-clinical data and re-
20 sults relating to a product or use that has not been ap-
21 proved, cleared, or licensed and is being investigated or
22 developed.”;

23 (4) in subparagraph (3), as redesignated—

24 (A) by striking “(A)”;

25 (B) by striking clause (B); and

1 (C) by striking “drug” each place it ap-
2 pears and inserting “drug or device”; and
3 (5) by adding at the end the following:
4 “(4) Nothing in this paragraph shall be construed to
5 limit the ability of manufacturers or sponsors of drugs or
6 devices to engage in communications or activities not spec-
7 ified in subparagraph (2) or (3) that are otherwise permis-
8 sible.”.

1 SEC. ____ . COMMUNICATIONS REGARDING INTENDED USES
2 OF DRUGS AND DEVICES; SCIENTIFIC EX-
3 CHANGE.

4 The Federal Food, Drug, and Cosmetic Act is amend-
5 ed by inserting after section 201 of such Act (21 U.S.C.
6 321) the following:

7 “SEC. 201A. INTENDED USES OF DRUGS AND DEVICES.

8 “(a) INTENDED USE.—For purposes of this Act, in-
9 cluding sections 301(d), 502(f)(1), 505, 510, 513, and
10 515, and for purposes of section 351 of the Public Health
11 Service Act, the intended use of a drug or device shall
12 not be determined by reference to—

13 “(1) actual or constructive knowledge of the
14 manufacturer or sponsor that such drug or device
15 will be used in a manner that varies from the use
16 approved, cleared, or licensed for marketing under
17 section 505, 510, 513, or 515 of this Act or section
18 351 of the Public Health Service Act;

19 “(2) non-public statements about the drug or
20 device that are not reflected in any claim, pro-
21 motional statement or material, or circumstances
22 surrounding the distribution of the drug or device
23 that involve interactions with third parties; or

1 “(3) communications meeting the criteria under
2 subsection (b) to be considered scientific exchange
3 safe harbor communications.

4 “(b) SCIENTIFIC EXCHANGE SAFE HARBOR.—

5 “(1) IN GENERAL.—A communication by a
6 manufacturer or sponsor, or a person acting on be-
7 half of a manufacturer or sponsor, about informa-
8 tion that is not included in the drug or device label-
9 ing required by this Act, constitutes a scientific ex-
10 change safe harbor communication if—

11 “(A) the communication is not advertising
12 or otherwise promotional in nature;

13 “(B) the communication is supported by
14 competent and reliable scientific evidence;

15 “(C) the communication clearly discloses
16 appropriate contextual information about the
17 data presented, including information about
18 limitations of the data, the scientific and ana-
19 lytical methodologies used, and any contradic-
20 tory data or information known to the manufac-
21 turer or sponsor;

22 “(D) the communication includes a con-
23 spicuous and prominent statement about such
24 information not being contained in the drug or
25 device labeling required by this Act; and

1 “(E) if the communication relates to a use
2 of a drug or device that has not been approved
3 or cleared for marketing under section 505,
4 510, 513, or 515 of this Act or section 351 of
5 the Public Health Service Act, the manufac-
6 turer or sponsor, or person acting on behalf of
7 the manufacturer or sponsor, makes no rep-
8 resentation that such use has been dem-
9 onstrated to be safe or effective.

10 “(2) RULE OF CONSTRUCTION.—Nothing in
11 this subsection shall be construed—

12 “(A) to authorize the Secretary to require
13 that a manufacturer or sponsor submit an ap-
14 plication, certification, or other such submis-
15 sion, or to seek the Secretary’s review or ap-
16 proval, before, during, or subsequent to engag-
17 ing in scientific exchange; or

18 “(B) to limit the ability of a manufacturer
19 or sponsor to engage in communications or ac-
20 tivities not specified in this subsection, but that
21 are otherwise permissible.”.

July 10, 2017

The Honorable Brett Guthrie
Vice-Chairman, Subcommittee on Health
Energy and Commerce Committee
2434 Rayburn House Office Building
Washington, DC 20515

Re: H.R. 2026 – The Pharmaceutical Information Exchange (PIE) Act of 2017

Dear Vice-Chairman Guthrie,

The undersigned organizations commend you for your leadership in introducing *H.R. 2026 – The Pharmaceutical Information Exchange (PIE) Act of 2017* which will improve patient access to emerging medication therapies and devices by codifying a safe harbor for certain health care economic and scientific information communications between biopharmaceutical and medical device manufacturers and population health decision makers. Collectively, our organizations represent population health decision makers (e.g. payers, provider sponsored health plans, pharmacy benefit managers, accountable care organizations, and integrated delivery networks), biopharmaceutical and medical device manufacturers, patient advocacy groups, health care providers, health economists, and others.

We support the need for timelier and more proactive sharing of preapproval health care economic information (HCEI) between biopharmaceutical and medical device manufacturers and population health decision makers to enable the implementation of value-based contracts, aid in forecasting and budgeting, and expedite coverage decisions for emerging therapies, including those granted breakthrough designation. The need for this proactive communication is especially important now as the United States health care system evolves from a fee-for-service payment system to a modernized system rewarding quality, improved patient outcomes, and value.

We support H.R. 2026 because it will:

- Create a legislative safe harbor to allow biopharmaceutical and medical device manufacturers to share proactively with population health decision makers truthful and not misleading clinical and economic information about medications and devices in the pipeline, as well as new uses of approved products, prior to FDA approval during the forecasting and rate setting process. A legislative safe harbor for PIE will confirm that the proactive dissemination of certain information does not violate the prohibitions against preapproval promotion and does not run afoul of the labeling, misbranding, and intended use provisions of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

- Facilitate communication from biopharmaceutical and medical device manufacturers to an appropriate audience of population health decision makers who need this information for financial forecasting and planning purposes only.
- Extend PIE to investigational products not approved/cleared for any use and investigational uses of approved/cleared products for which there is an intent to file a supplement. The rationale for PIE applies equally to both. Factors such as product information, indication sought, clinical data, anticipated approval timeline, pricing information, targeting/marketing strategies and product related programs or services are unique to each indication. Anticipating a new indication and properly planning for the impact on budget and expansion of patient populations eligible to receive such medication or device are vital for population health decision makers.
- Allow for bidirectional exchange of information and sharing of health care economic or scientific information. Such information would include data from pivotal clinical trials, pharmacoeconomic data, as well as data relating to patient centered outcomes (health related quality of life, treatment satisfaction, etc.), and could also include other material items, such as anticipated indications, place in therapy, and routes of administration.

In summary, our organizations believe that furthering communications between biopharmaceutical and medical device manufacturers and population health decision makers prior to FDA approval/clearance will help to shift the United States health care system to a focus on value and promote good outcomes for patients. Thank you for championing this very important issue and please use our organizations as a resource as you continue to lead this initiative forward.

Sincerely,

Academy of Managed Care Pharmacy (AMCP)
 Amgen
 Blue Cross and Blue Shield Association (BCBSA)
 Bristol-Myers Squibb
 Center for the Evaluation of Value and Risk in Health, Tufts Medical Center
 Cigna
 Dymaxium, Inc.
 Genentech, Inc.
 Gilead Sciences
 Harvard Pilgrim Health Care
 Humana
 International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
 Mayo Clinic
 Pharmaceutical Research and Manufacturers of America (PhRMA)
 Precision for Value
 Qualchoice Health Plan Services, a division of Catholic Health Initiatives
 Sanofi
 Takeda
 University of Utah College of Pharmacy, Pharmacotherapy Outcomes Research Center
 Xcenda



Sound Policy. Quality Care.

May 2, 2017

The Honorable Morgan Griffith
2202 Rayburn House Office Building
Washington, D.C. 20515

RE: Support for the "Medical Product Communications Act of 2017" (H.R. 1703)

Dear Congressman Griffith:

The Alliance of Specialty Medicine (the "Alliance") represents more than 100,000 specialty physicians. The Alliance is deeply committed to improving access to specialty medical care through the advancement of sound health policy.

The undersigned members of the Alliance are writing to thank you for your introduction of H.R. 1703, the Medical Product Communications Act of 2017. The current regulatory paradigm to determine a product's "intended use" by the Food and Drug Administration (FDA) has created uncertainty among manufacturers, which in turn hampers the free exchange of information.

For some specialties, a so-called "off-label" use – or use of a medicine or device for an indication not approved by FDA – is the standard of care. As such, the free flow of data on such off-label uses is critical to advancement of the practice of medicine. Unfortunately, the current way FDA determines the "intended use" has a negative impact on such scientific exchange.

Your legislation would establish clear parameters on what constitutes a "scientific exchange" by which a manufacturer could, within defined limitations, share data related to an unapproved indication. We believe that H.R. 1703 strikes the right balance between placing reasonable and sound limits on manufacturers and allowing a productive, scientific exchange of data that will benefit patients.

In closing, we thank you for your commitment to this important issue and stand ready to help you advance the Medical Product Communications Act of 2017. Please do not hesitate to contact us should you have any questions or require additional information.

Sincerely,

American Association of Neurological Surgeons
American College of Mohs Surgery
American College of Osteopathic Surgeons
American Gastroenterological Association
American Society for Dermatologic Surgery Association
American Society of Cataract and Refractive Surgery
American Society of Echocardiography
American Society of Plastic Surgeons
American Urological Association
Coalition of State Rheumatology Organizations
Congress of Neurological Surgeons



May 16, 2017

The Honorable Morgan Griffith
2202 Rayburn House Office Building
Washington, DC 20515

RE: Support for H.R. 1703, the "Medical Product Communications Act of 2017"

Dear Congressman Griffith,

The Dystrophic Epidermolysis Bullosa Research Association of America (debra of America) is the only U.S. nonprofit providing all-inclusive support to the Epidermolysis Bullosa (EB) community by engaging in two initiatives in parallel. We fund innovative research for a treatment and a cure and provide free programs and services for those with EB. We call EB "the worst disease you've never heard of"—it is a rare connective tissue disorder with many genetic and symptomatic variations that affects 1 out of every 20,000 births in the U.S.

We, and other members of the Rare Disease community, often find ourselves with few, if any, treatment options. In fact, of the more than 7,000 rare diseases, very few have FDA approved treatment options. According to Global Genes, a leading rare disease patient and organizational advocacy group, only five percent of rare diseases have a FDA approved treatment. While we would like nothing more than to see that landscape change, now most rare disease patients, including those with EB, are receiving off-label treatments out of necessity—if they are lucky. With 1 in 10 Americans suffering from a rare disease, H.R. 1703 has the potential to improve treatment options for a large number of patients. We want to thank you for your leadership on this issue and introducing H.R. 1703.

Off-label use is often considered the standard of care for many rare diseases and their respective patients; therefore, it is imperative that more comprehensive information pertaining to off-label use be shared in a way that can best benefit patients, potentially providing more treatment options. This sharing of this comprehensive information would potentially provide more treatment options from off-label usage. Currently, the FDA's determination of "intended use" negatively impacts scientific exchange of information that could be beneficial or even potentially life-changing to patients. We believe H.R. 1703 appropriately balances patient safety while providing patients and their physicians access to appropriate, evidence-based information used to make informed treatment choices.

Dystrophic Epidermolysis Bullosa Research Association of America, Inc.

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Brett Kopelan, M.A., Executive Director

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The undersigned organizations thank you for your commitment to this issue and stand ready to help you advance the Medical Product Communications Act of 2017.

Sincerely,

Association for Creatine Deficiencies
 Bridge the Gap-SYNGAP Education and Research Foundation
 Choroideremia Research Foundation
 Dystrophic Epidermolysis Bullosa Research Association of America, Inc.
 Foundation for Sarcoidosis Research
 Gastroparesis Patient Association for Cures and Treatments, Inc.
 Global Genes—Allies in Rare Disease
 Fibrous Dysplasia Foundation
 Jonah's Just Begun-Foundation to Cure Sanfilippo, Inc.
 Little Miss Hannah Foundation
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 MLD Foundation
 Neuromuscular Disease Foundation
 NGLY1
 Noah's Hope
 Pathways for Rare and Orphan Studies
 Phelan-McDermid Syndrome Foundation
 RASopathies Network
 United Leukodystrophy Foundation

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May 5, 2017

The Honorable Greg Walden
Chairman
Committee on Energy and Commerce
Washington D.C. 20515

The Honorable Frank Pallone
Ranking Member
Committee on Energy and Commerce
Washington D.C. 20515

The Honorable Michael C. Burgess, M.D.
Chairman
Subcommittee on Health
Committee on Energy and Commerce
Washington D.C. 20515

The Honorable Gene Green
Ranking Member
Subcommittee on Health
Committee on Energy and Commerce
Washington D.C. 20515

Dear Chairmen and Ranking Members:

The members of the Healthcare Leadership Council (HLC) strongly support H. R. 1703, the "Medical Product Communications Act." We urge the Energy and Commerce Committee to take up this bill for consideration and approve it. HLC members, through our broad, multisector National Dialogue for Healthcare Innovation (NDHI) have emphasized the need to increase flexibility to share scientific and healthcare economic information with healthcare decision-makers in order to drive the use of the highest-value treatment option.

HLC is a coalition of chief executives from all disciplines within American healthcare. It is the exclusive forum for the nation's healthcare leaders to jointly develop policies, plans, and programs to achieve their vision of a 21st century health system that makes affordable, high-quality care accessible to all Americans. Members of HLC—hospitals, academic health centers, health plans, pharmaceutical companies, medical device manufacturers, biotech firms, health product distributors, pharmacies, post-acute care providers, and information technology companies—believe that the issue of healthcare costs should be addressed through competition in a transparent, consumer-oriented healthcare marketplace.

HLC believes that biopharmaceutical manufacturers can and should partner with payers and providers in efforts to communicate about and optimize the clinical benefits of prescribed treatments. The push for value-based payment is accelerating demands by payers and providers for a growing range of information about the clinical and economic outcomes of biopharmaceutical products. Biopharmaceutical companies routinely develop data describing the cost-effectiveness of various treatment options, data based on post-market use of these medicines, as well as safety and efficacy information. Application of these data can enhance patient care and the efficiency of the healthcare system, but companies are not currently permitted to share such information proactively with healthcare professionals or payers.

As leaders from the full spectrum of American healthcare, we have long maintained that driving high-value healthcare must be a priority. Doctors should have the most up-to-date information when caring for their patients and, when done responsibly and in an appropriate context, manufacturers should be able to provide it. Meaningful, fact-based discussions between healthcare product manufacturers and the purchasers of their products will help drive the adoption of better and safer patient care.

We applaud your leadership in reviewing important legislation to further these goals. Please feel free to contact HLC's SVP for Policy, Tina Grande (tgrande@hlc.org or 202-449-3433), with any questions.

Sincerely,



Mary R. Grealy
President



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

July 11, 2017

The Honorable Michael Burgess
Chairman, Health Subcommittee
and
The Honorable Gene Green
Ranking Member, Health Subcommittee
Committee on Energy and Commerce
U.S. House of Representatives
2125 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Burgess and Ranking Member Green:

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, respectfully submits the following comments for the record for your subcommittee's July 12 hearing, *Examining Medical Product Manufacturer Communications*, which will include a discussion of draft legislation titled "Communications Regarding Intended Uses of Drugs and Devices; Scientific Exchange" and "Facilitating Exchange of Information Prior to Approval."

We urge your subcommittee to oppose both pieces of draft legislation because they include provisions that, would significantly expand marketing for unapproved uses of drugs and medical devices that have been approved or cleared by the Food and Drug Administration (FDA) for at least one use. These bills would threaten patient health and safety by undermining the current regulatory regimes for ensuring that drugs and medical devices are safe and effective for each intended use. Similar legislation was considered by Congress during the drafting of the 21st Century Cures Act but was wisely rejected because of its controversial nature.

As the FDA recently articulated, the existing regulatory restrictions on manufacturer communications regarding unapproved uses of approved or cleared medical products are overwhelmingly justified by the substantial government interest in protecting patient health and safety. These restrictions advance health and safety by:

- motivating the development of robust scientific data on safety and effectiveness for each new use of a medical product;
- maintaining the premarket review process for safety and effectiveness of each intended use in order to prevent harm; protect against fraud, misrepresentation, and bias; and prevent the diversion of health care resources to ineffective treatments;
- ensuring that required product labeling is accurate and informative;
- protecting the integrity and reliability of promotional information regarding medical product uses;

Public Citizen

July 11, 2017 Letter to the Health Subcommittee
of the House Committee on Energy and Commerce

- protecting human subjects who are receiving experimental treatments, ensuring informed consent, and maintaining incentives for clinical trial participation;
- protecting innovation incentives, including statutory grants of exclusivity; and
- promoting the development of products for underserved patients.¹

Together, these interests support the FDA's overarching mission of protecting and promoting public health. That interest outweighs any purported public health benefit of allowing manufacturer communications regarding unapproved uses of medical products.

Dangers of Promotion for Unapproved Uses

Although the FDA approves new drugs and some medical devices before they are marketed, it—and the public—maintains a strong interest in evaluating the products' safety and effectiveness for any additional uses that were not evaluated at the time of initial approval. For example, a drug that poses a serious risk to the patient's immune system may merit approval to treat cancer but not to treat a headache. Thus, the FDA does not evaluate safety in a vacuum: For each proposed use, the agency balances the drug's risk of harm against its potential for benefit. Furthermore, the government has a powerful interest in ensuring that a drug is not only safe for each use for which a manufacturer markets it, but also effective. Marketing for a safe but ineffective use can have detrimental health effects if it diverts patients from effective treatment.² Moreover, a drug's safety for a second use is not established once a drug has been approved (and thus deemed safe and effective) for a first use. To the contrary, a drug that is safe for one use can be life-threatening for another.

Although prescribing drugs and devices for unapproved uses is common, scientific evidence supporting most such uses often is lacking. For example, a recent study conducted in Canada found that the vast majority of off-label uses—81 percent—lacked strong scientific evidence of effectiveness.³ Patients who received a prescription for an off-label use lacking strong evidence of effectiveness were 54 percent more likely to experience an adverse drug reaction that resulted in stopping use of the drug than were those who were prescribed a drug for an approved use. The increased risk of serious adverse events when drugs are prescribed for off-label uses, combined with the lack of strong evidence of benefit, demonstrates that a favorable risk–benefit relationship has not been established for most off-label uses of drugs and further supports strong restrictions against promotion of unapproved uses.

¹ FDA. Memorandum: Public health interests and first amendment considerations related to manufacturer communications regarding unapproved uses of approved or cleared medical products. January 2017. Available at <https://www.regulations.gov/contentStreamer?documentId=FDA-2016-N-1149-0040&attachmentNumber=1&contentType=pdf>. Accessed May 30, 2017. At 3-16.

² *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998) (noting evidence that off-label use of calcium channel blockers deprived patients of more effective treatments).

³ Eguale T, Buckeridge DL, Verma A, et al. Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med.* 2016;176(1):55-63.

Even Relying on Peer-Reviewed Scientific Journal Articles Can be Dangerous

Subsection (b) (Scientific Exchange Safe Harbor) of proposed Section 201A in the draft legislation titled “Communications Regarding Intended Uses of Drugs and Devices; Scientific Exchange” is particularly troubling because it would allow pharmaceutical and medical device manufacturers to disseminate a broad range of information related to unapproved uses in both the scientific and lay media. In this way, the bill would radically extend the types of information that can be disseminated by manufacturers beyond what is currently permitted under the FDA’s January 2009 guidance for industry on good reprint practices⁴ and its more expansive February 2014 draft guidance on distributing scientific and medical publications concerning unapproved new uses.⁵

It is important to recognize that the FDA’s current policy of allowing distribution of peer-reviewed journal articles about unapproved uses already allows companies to market drugs based on unreliable and in some cases deceptive evidence of safety and effectiveness. First, published peer-reviewed articles represent a partial, and often biased, sample of all medical evidence regarding the safety and effectiveness of medical products. For example, a 2008 study of antidepressant drug clinical trials submitted to the FDA found that 97 percent of all trials with positive results had been published, but only 39 percent of the trials deemed by the FDA to have negative or “questionable” results had been published.⁶

Second, even among the most respected journals, the peer-review process suffers from shortcomings that can permit fraudulent or otherwise misleading articles to find their way into publication and then, via drug salespeople, into doctors’ hands. Unlike the rigorous FDA review process for drugs and high-risk medical devices, the peer-review process for scientific and medical journals generally is not well equipped to uncover the wide range of problems that can undermine the integrity of clinical trial data, including outright fraud, flawed study design, failure to adhere to protocol-specified procedures, poorly conducted statistical analyses, and incomplete reporting of key data. Conflicts of interest resulting from financial relationships between authors of peer-reviewed journal articles and manufacturers can increase the likelihood of such problems. And most busy physicians and other health care providers are even less equipped than journal peer reviewers to assess the validity and reliability of data presented in journal articles that are distributed by manufacturers.

⁴ FDA. Good reprint practices for the distribution of medical journal articles and medical or scientific reference publications on unapproved new uses of approved drugs and approved or cleared medical devices: Guidance for industry. January 2009. <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>. Accessed May 30, 2017.

⁵ FDA. Revised draft guidance for industry: Distributing scientific and medical publications on unapproved new uses—recommended practices. Feb 2014. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm387652.pdf>. Accessed May 30, 2017.

⁶ Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med*. 2008;358(3):252-260.

Public Citizen

July 11, 2017 Letter to the Health Subcommittee
of the House Committee on Energy and Commerce

To underscore the limitations of relying on peer-reviewed scientific and medical journals, the FDA recently explained the following:

Although some of the assurances from independent review for a particular study can be obtained by review by non-governmental entities (such as peer review coordinated by a scientific or medical journal), the standards governing FDA review provide an assurance of data completeness, scientific rigor, and a thoroughness of evaluation that are not met by the more narrow examination of the peer review process, given the limited data typically available to and reviewed by peer reviewers, the more limited number of peer reviewers (and thus more limited areas of expertise), and the scope of a journal article.⁷

Relying on articles published in peer-reviewed journals without digging deeper into the underlying data — as occurs when FDA scientists review new drug applications, medical device pre-market approval applications, and some 510(k) device pre-market clearance applications — can lead to the rapid adoption of ineffective or unsafe unapproved uses of drugs and medical devices and, thus, put patients in harm's way. And reliance on other types of "scientific" information, such as letters to the editor and information published in the lay media, would be even more dangerous.

Enclosed are more detailed comments on this topic that we submitted to the FDA on April 19, 2017.

Critique of Subsection (b) (Scientific Exchange Safe Harbor) of Proposed Section 201A under the Draft Legislation, "Communications Regarding Intended Uses of Drugs and Devices; Scientific Exchange"

One factor that would define the boundaries of the scientific exchange safe harbor under subsection (b) of proposed Section 201A is that "the communication is not advertising or otherwise promotional in nature." A second factor is that "if the communication relates to a use of a drug or device that has not been approved or cleared for marketing..., the manufacturer or sponsor, or person acting on behalf of the manufacturer or sponsor, makes no representation that such use has been demonstrated to be safe or effective." Yet Congress needs to understand that the primary reason drug and device company representatives distribute scientific and medical information regarding unapproved uses is, indisputably, to promote those uses to physicians and other health care providers in the hope of increasing prescribing of the companies' products. By their very nature, these communications are promotional.

A third factor that would define the boundaries of the scientific exchange safe harbor is that "the communication is supported by competent and reliable scientific evidence." The meaning of "competent and reliable scientific evidence" here is unclear. Moreover, for the reasons discussed above, evidence from articles published in peer-reviewed journals that may appear to be competent and reliable may be seriously flawed.

⁷ FDA Memorandum, *supra* note 1, at 9.

Public Citizen

July 11, 2017 Letter to the Health Subcommittee
of the House Committee on Energy and Commerce

Finally, for a scientific exchange communication to qualify for the safe harbor under subsection (b) of proposed Section 201A, it would have to clearly disclose “appropriate contextual information about the data presented, including information about limitations of the data, the scientific and analytical methodologies used, and any contradictory data or information known to the manufacturer or sponsor.” However, limitations of scientific data can easily go unrecognized or be disregarded, and the lack of contradictory information may reflect a failure to conduct appropriate additional research or rigorously search for such information.

Conclusion

History shows that after-the-fact enforcement of safety and efficacy standards for marketing of drugs and devices is inadequate to protect patient safety. Rather, when an unproven assertion of safety and effectiveness is relied on to market a medical product, the resulting harm may be severe—even life-threatening.

Public Citizen urges you to oppose the draft legislation that is to be discussed at your subcommittee’s hearing tomorrow and any similar controversial legislation that is introduced in the future.

Thank you for the opportunity to submit these comment for the record on these important public health matters.

Sincerely,



Michael Carome, M.D.
Director
Public Citizen’s Health Research Group

Enclosure

cc: Members of the Health Subcommittee, Committee on Energy and Commerce



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

April 19, 2017

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

**COMMENTS ON
MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES
OF APPROVED OR CLEARED MEDICAL PRODUCTS
Docket No. FDA-2016-N-1149**

Public Citizen, a consumer organization with members and supporters nationwide, submits these comments in response to the request for comment on “Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products,” published in the Federal Register by the Food and Drug Administration (FDA) on September 1, 2016. Primarily through its Health Research Group, Public Citizen has long been an advocate for strong regulation of drugs and medical devices for the protection of patients. Public Citizen appreciates the agency’s attention to this important public health issue and the opportunity to provide these comments.

At least since the 1990s, pharmaceutical and medical device companies have been pushing back against FDA restrictions on marketing drugs and medical devices for uses not approved by the agency. After only limited initial success, the industry recently stepped up its efforts to roll back these restrictions. At its heart, the industry push challenges two central tenets of the FDA regulatory scheme: (1) objective scientific evaluation of evidence concerning each proposed use of a drug or device is needed to protect consumers and (2) selling drugs and devices for therapeutic uses in the absence of validation by such evaluation is false or misleading. The development of appropriate policy in this area requires an understanding of the development of the FDA’s regulatory authority. Accordingly, we begin with a short historical summary. We then discuss the risks to patients when manufacturers promote their products for unapproved uses and the unreliability of journal articles as a basis for physicians’ decisionmaking. Finally, we explain that the First Amendment does not support the industry call for relaxation of the restrictions on promoting products for uses that the FDA has not approved as safe and effective for patients.

BACKGROUND, FDA’S RESPONSIBILITY, AND SUBSTANTIAL GOVERNMENT INTERESTS

The current regulatory regimes for drugs and medical devices developed in response to real-world situations that highlighted the need for an objective decisionmaker to assess the safety

and effectiveness of a drug or device before it is sold to patients. Congress took the first step in 1906, passing the Pure Food and Drugs Act, partially in response to cure-all claims for worthless and dangerous medicines.¹ The law prohibited the sale of misbranded or adulterated drugs but required no premarketing review and no prior testing or showing of safety. And to force a drug off the market, the government bore the burden of proving that the product's labeling was false and misleading.²

Then, in 1937, 105 people died from taking Elixir Sulfanilamide, a liquid form of the first sulfa antibiotic. The elixir was marketed without toxicity testing of the ingredients, which included the toxic chemical diethylene glycol.³ This incident prompted passage of the 1938 Food, Drug, and Cosmetic Act (FDCA), which required manufacturers to submit premarket notifications demonstrating the safety of each new drug before marketing. Specifically, the law required the manufacturer of a "new drug"—that is, a drug "not generally recognized, among experts ... as safe and effective for use"—to submit to the FDA, in advance of marketing a new product, a "new drug application" (NDA) demonstrating "adequate testing" showing that the drug is safe for "use under the conditions prescribed" in its labeling.⁴ The law thus prohibited, for the first time, marketing a new drug for any use not approved by the FDA.

A near miss in 1960 prompted another important improvement in drug regulation. The FDA considered but ultimately refused to approve thalidomide. The drug was marketed in Europe and elsewhere for insomnia and morning sickness in pregnant women, and subsequently was found to cause severe human birth defects.⁵ The tragedy sparked congressional hearings, which revealed that drug companies were making effectiveness claims that were unsupported or based on shoddy scientific evidence.⁶ In 1962, Congress responded by strengthening the drug approval process to require not only proof of safety, but also "substantial evidence" of effectiveness for a drug's intended use.⁷ This evidence must be supported by "adequate and well-controlled investigations."⁸ Moreover, because a drug may be safe and effective for one use but unsafe or ineffective for another, the law requires a manufacturer of a drug that has already been approved through an NDA to submit a supplemental NDA demonstrating the drug's safety and effectiveness for any additional use before labeling or marketing the drug for that new use.⁹ The

¹ Janssen W. Outline of the History of U.S. Drug Regulation & Labeling. *Food Drug Cosm. L.J.* 1981;36:420, 422.

² 21 U.S.C. § 352(a); Richard A. Merrill, *The Architecture of Gov't Regulation of Med. Prods.*, 82 Va. L. Rev. 1753, 1761 (1996).

³ Wax P. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. *Ann Intern Med.* 1995;122:456–461.

⁴ 21 U.S.C. §§ 321(p), 355(a), (b), (d).

⁵ Avorn J. Learning about the safety of drugs—a half-century of evolution. *New Engl J Med.* 2011;365:2151–2153.

⁶ FDA. Promoting Safe and Effective Drugs for 100 Years. Available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDAConsumer/ucm093787.htm>.

⁷ 21 U.S.C. §§ 321(p), 355(a), (b), (d).

⁸ *Id.* § 355(d).

⁹ See 21 C.F.R. § 314.70.

requirement of adequate and well-controlled studies was “revolutionary” and invaluable in advancing pharmaceutical safety and effectiveness.¹⁰

The 1938 and 1962 laws protect patients by mandating a review process that enables the FDA to detect unsafe or ineffective medicines *before* they reach consumers and cause harm. The resulting premarket approval process is a cornerstone of modern drug safety regulation, serving the separate but complementary goals of protecting the public from dangerous drugs and preventing false and misleading claims.¹¹ Indeed, “[t]here are few, if any, more important functions performed by any regulatory agency than ... ensuring that when a citizen takes a prescription drug, that individual has absolute assurance that the product is safe and effective for the condition for which his physician has prescribed it.”¹² The premarket review process is a crucial bulwark against the sorts of pseudo-scientific claims that characterized fraudulent medicine before federal regulation.

As the FDA recognizes, existing restrictions on manufacturer communications regarding unapproved uses of approved or cleared medical products are overwhelmingly justified by “substantial government interests related to health and safety,” including, in particular, the following:

- motivating the development of robust scientific data on safety and effectiveness for each new use of a medical product;
- maintaining the premarket review process for safety and effectiveness of each intended use in order to prevent harm; protect against fraud, misrepresentation, and bias; and prevent the diversion of health care resources to ineffective treatments;
- ensuring required product labeling is accurate and informative;
- protecting the integrity and reliability of promotional information regarding medical product uses;
- protecting human subjects who are receiving experimental treatments, ensuring informed consent, and maintaining incentives for clinical trial participation;
- protecting innovation incentives, including statutory grants of exclusivity; and
- promoting the development of products for underserved patients.¹³

¹⁰ Promoting safe and effective drugs for 100 years. FDA Consumer Magazine. Jan–Feb 2006. Available at www.fda.gov/AboutFDA/WhatWeDo/History/CentennialofFDA/CentennialEditionofFDAConsumer/ucm093787.htm. [Last accessed Mar. 9, 2017]

¹¹ See *Abigail Alliance for Better Access to Dev'l Drugs v. von Eschenbach*, 495 F.3d 695, 703 (D.C. Cir. 2007) (en banc).

¹² See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 69 (D.D.C. 1998), *vacated on other grounds*, *Wash. Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000).

¹³ FDA. Memorandum: Public health interests and first amendment considerations related to manufacturer communications regarding unapproved uses of approved or cleared medical products. Jan 2017. Available at <https://www.regulations.gov/contentStream?documentId=FDA-2016-N-1149-0040&attachmentNumber=1&contentType=pdf>. [Last accessed Feb. 28, 2017] at 3-16.

Public Citizen

April 19, 2017
 Comments on FDA Draft Guidance
 Docket No. FDA-2016-D-1149

Together, these interests support the FDA's overarching mission of protecting and promoting public health. That interest outweighs any purported public health benefit of allowing manufacturer communications regarding unapproved uses of medical products.

DANGERS OF PROMOTION FOR UNAPPROVED USES

Although the FDA today approves new drugs and some medical devices before they are marketed, it—and the public—maintains a strong interest in evaluating the products' safety and effectiveness for any additional uses that were not evaluated at the time of initial approval. For example, a drug that poses a serious risk to the patient's immune system may merit approval to treat cancer but not to treat a headache. Thus, the FDA does not evaluate safety in a vacuum: For each proposed use, the agency balances the drug's risk of harm against its potential for benefit. Furthermore, the FDA has a powerful interest in ensuring that a drug is not only safe for each use for which a manufacturer markets it, but also effective. Marketing for a safe but ineffective use can have detrimental health effects if it diverts patients from effective treatment.¹⁴

Moreover, a drug's safety for a second use is not established once a drug has been approved (and thus deemed safe and effective) for a first use. To the contrary, a drug that is safe for one use can be life threatening for another. For example, the drug bromocriptine is safe for use in treating certain diseases, such as Parkinson's disease, but has been linked to strokes when used to suppress lactation in postpartum women. See 59 Fed. Reg. 43347 (1994) (FDA notice of withdrawal of approval for use to suppress lactation); FDA, http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/017962s065s068lbl.pdf, at 4, 11 (current product labeling, listing approved uses and warning against use by lactating women).

Accordingly, it is not surprising that harms associated with taking marketed drugs for unapproved uses have been well-documented. For example, starting in the mid-1980s, doctors increasingly prescribed estrogen-progestin hormone replacement drugs to postmenopausal women as a preventative measure against a range of illnesses, including heart disease, breast cancer, and Alzheimer's disease—uses that were not FDA-approved. After tens of millions of prescriptions had been written, a large, U.S. government-funded randomized clinical trial found that such unapproved uses of the drugs significantly increased risks of coronary heart disease, stroke, pulmonary embolism, and invasive breast cancer, and that these risks exceeded the drugs' benefits when prescribed for several off-label uses.¹⁵

Unfortunately, this example is just one of many.¹⁶ Risperdal, Xyrem, Avandia, Zofran, and Neurontin are other well-known examples of drugs that caused significant injury as a result

¹⁴ See *Friedman*, 13 F. Supp. 2d at 56–57 (noting evidence that off-label use of calcium channel blockers deprived patients of more effective treatments).

¹⁵ Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. *JAMA*. 2002;288:366-368; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321-333.

¹⁶ See also, e.g., *Perry v. Novartis Pharm. Corp.*, 456 F. Supp. 2d 678 (E.D. Pa. 2006) (Elidel approved as safe and effective to treat dermatitis, but poses risk of causing cancer when used off-label in patients less than two years old);

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of the manufacturers' off-label promotion and marketing. And the problem is not limited to drugs, as demonstrated by the hundreds of patients seriously injured by unapproved uses of Medtronic, Inc.'s Infuse medical device.¹⁷

Although prescribing drugs and devices for unapproved uses is common, scientific evidence supporting most such uses is lacking. For example, an observational study published in 2008 examined the frequency with which drugs were prescribed for unapproved uses in the U.S. from January 2005 to June 2007.¹⁸ The researchers found that, for the 25 drugs prescribed most frequently for unapproved uses that have inadequate evidence of effectiveness, 29 percent of the total prescriptions were for unapproved uses. Collectively, for these 25 drugs, scientific evidence was inadequate to support the effectiveness of the drugs for 82 percent of their off-label uses.

A more recent observational study conducted in Canada likewise found that the vast majority of off-label uses—81 percent—lacked strong scientific evidence of effectiveness.¹⁹ Patients who received a prescription for an off-label use lacking strong evidence of effectiveness were 54 percent more likely to experience an adverse drug reaction that resulted in stopping use of the drug than those who were prescribed a drug for an approved use.

The increased risk of serious adverse events when drugs are prescribed for off-label uses, combined with the lack of strong evidence of benefit, demonstrates that a favorable risk–benefit relationship has not been established for most off-label uses of drugs and further supports strong restrictions against promotion of unapproved uses.

In addition, allowing broad promotion of drugs for unapproved uses would deter clinical trials of unapproved uses. Manufacturers would not invest in expensive testing of new uses if they were free to market their products for those uses without evidence of benefit. As a result, physicians, patients, and the FDA would be deprived of important information about safety and effectiveness.

Friedman, 13 F. Supp. 2d at 56–57 (noting off-label prescriptions of anti-arrhythmic drugs encainide and flecainide to treat minor heart-rhythm disturbances in patients with recent heart attacks caused an estimated 3,000 to 10,000 patient deaths per year); *see generally* Henry A. Waxman, *A History of Adverse Drug Experiences: Congress Had Ample Evidence to Support Restrictions on the Promotion of Prescription Drugs*, 58 Food & Drug L.J. 299, 301–06 (2003) (detailing history of harms resulting from marketing of drugs for uses for which they had not been shown to be safe and effective).

¹⁷ *See Patients who received Medtronic's Infuse product to get \$8.45 million in settlements*, StarTribune, Aug. 2, 2016 ("Claims of injuries from such 'off-label' use have plagued Infuse almost from the time of its introduction into the market in 2002."); *Medtronic Says Device for Spine Faces Probe*, Wall St. J., Nov. 19, 2008 (describing Department of Justice probe into Medtronic's off-label promotion).

¹⁸ Walton SM, Schumock GT, Lee KV, et al. Prioritizing future research on off-label prescribing: Results of a quantitative evaluation. *Pharmacotherapy*. 2008;28(12):1443-1452.

¹⁹ Egale T, Buckeridge DL, Verma A, et al. Association of off-label drug use and adverse drug events in an adult population. *JAMA Intern Med*. 2016;176(1):55-63.

MARKETING TECHNIQUES EXACERBATE THE RISKS

In its January 2009 guidance for industry on good reprint practices²⁰ and its more expansive February 2014 draft guidance on distributing scientific and medical publications on unapproved new uses,²¹ the FDA articulated “safe harbor” policies that permit pharmaceutical and medical device manufacturers to disseminate scientific and medical journal articles and other materials describing unapproved uses of approved or cleared medical products, provided certain conditions are met. These guidelines allow drug companies to engage in public discourse and scientific debate, while addressing (although not wholly solving) the most common problems resulting from unregulated marketing of drugs for unapproved uses. For example, the guidelines attempt to address the problem of incomplete, skewed, or biased data by stating that reprints should be accompanied by a disclosure that identifies any conflicts of interest and by limiting a manufacturer’s distribution of publications funded by, written at the request of, or influenced by the manufacturer. They also include additional provisions designed to ensure that distributed information is scientifically sound, stating, for example, that reprints should address well-controlled studies and be published in a generally available, peer-reviewed journal.²²

Nonetheless, the FDA’s policy of allowing distribution of peer-reviewed journal articles about unapproved uses allows companies to market drugs based on unreliable and in some cases deceptive evidence of safety and effectiveness. The FDA guidelines state that, if manufacturers distribute articles or other information as set forth in the guidance, the FDA does not intend to use such distribution as evidence of the manufacturer’s “intent that the product be used for an unapproved new use” in violation of the FDCA. Yet the agency cannot overlook that the primary reason drug and device company representatives distribute scientific and medical information regarding unapproved uses undoubtedly is to promote those uses to physicians and other health care providers in the hope of increasing prescribing of the companies’ products. Legalized off-label marketing—even under the safe-harbor conditions specified in FDA guidance—threatens the U.S. regulatory process for ensuring that prescription drugs and medical devices are safe and effective for their intended uses.

Peer-reviewed scientific and medical journals vary significantly in their credibility and rigor. But even among the most respected journals, the peer-review process suffers from shortcomings that can permit fraudulent or otherwise misleading articles to find their way into publication and then, via drug salespeople, into doctors’ hands. Unlike the rigorous FDA review process for drugs and high-risk medical devices, the peer-review process for scientific and medical journals generally is not well equipped to uncover the wide range of problems that can undermine the integrity of clinical trial data, including outright fraud, flawed study design,

²⁰ FDA. Good reprint practices for the distribution of medical journal articles and medical or scientific reference publications on unapproved new uses of approved drugs and approved or cleared medical devices: Guidance for industry. Jan. 2009. Available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>. [Last accessed Mar. 9, 2017]

²¹ FDA. Revised draft guidance for industry: Distributing scientific and medical publications on unapproved new uses—recommended practices. Feb. 2014. Available at <http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm387652.pdf>. [Last accessed Mar. 9, 2017]

²² *Id.*

failure to adhere to protocol-specified procedures, poorly conducted statistical analyses, and incomplete reporting of key data. Conflicts of interest resulting from financial relationships between authors of peer-reviewed journal articles and manufacturers can increase the likelihood of such problems. And most busy physicians and other health care providers are even less equipped than journal peer reviewers to assess the validity and reliability of data presented in journal articles that are distributed by manufacturers.

Underscoring the limitations of relying on peer-reviewed scientific and medical journals, the FDA recently explained:

Although some of the assurances from independent review for a particular study can be obtained by review by non-governmental entities (such as peer review coordinated by a scientific or medical journal), the standards governing FDA review provide an assurance of data completeness, scientific rigor, and a thoroughness of evaluation that are not met by the more narrow examination of the peer review process, given the limited data typically available to and reviewed by peer reviewers, the more limited number of peer reviewers (and thus more limited areas of expertise), and the scope of a journal article.²³

Relying on articles published in peer-reviewed journals without digging deeper into the underlying data—as occurs when FDA scientists review new drug applications, medical device premarket approval applications, and some 510(k) device premarket clearance applications—can lead to the rapid adoption of ineffective or unsafe unapproved uses of drugs and medical devices and, thus, put patients in harm’s way.

Research Fraud and Misconduct — Research fraud and misconduct represent the most serious threat to the integrity of data presented in journal articles. The FDA itself has noted that fraud and misconduct have occurred in all phases of clinical research and have involved enrolling unqualified subjects, backdating information, fabricating data from tests that were not performed, failing to report adverse events, deviating from protocols, covering up mistakes, and submitting false data for publication.²⁴

Evidence suggests that the incidence of detected research fraud and misconduct, although very low, has increased significantly. For example, a 2012 study of the PubMed database found that the percentage of scientific articles retracted due to fraud had increased approximately tenfold since 1975.²⁵ Fraud or suspected fraud were the most commonly identified reasons for retraction of an article, occurring in 43 percent of cases. The study authors noted that “the current number of articles retracted because of fraud represents an underestimation of the actual number of fraudulent articles in the literature.”

²³ FDA Memorandum, *supra* note 13, at 9.

²⁴ Hamrell MR. Raising suspicions with the Food and Drug Administration: Detecting misconduct. *Sci Eng Ethics*. 2010;16(4):967-704.

²⁵ Fang FC, Steen RG, Casadevall A. Misconduct accounts for the majority of retracted scientific publications. *PNAS*. 2012;109(42):17028-17033. (Correction: *PNAS*. 2013;110(3):1137.)

Biased Study Design — Equally insidious and far more widespread than outright research fraud are a wide range of practices that result in clinical trial bias. In a 2015 editorial in the *Mayo Clinic Proceedings*, Prasad and Berger coined the term “hard-wire bias” to describe sources of potential bias originating in the initial design of randomized, double-blind clinical trials.²⁶ They pointed out that hard-wire bias cannot be corrected by using statistical methods or reanalysis. Examples described by the authors include selection bias and unequal-comparison bias.

Selection bias can occur when inclusion and exclusion criteria result in a very narrowly defined subject population, which prevents the generalizability of the results to a broader patient population, even though results of clinical trials routinely are used to justify use of a drug in a broader population.²⁷ Unequal-comparison bias stems from designs that disadvantage one trial group relative to another, such as selecting an active comparator for the control group that is not consistent with standard-of-care treatment.

Publication Bias — Another well-documented problem that adversely affects the scientific and medical literature is publication bias—the tendency of investigators to submit, and the tendency of editors and reviewers to accept, manuscripts with positive research findings. A 2009 systematic review by the Cochrane Library of studies assessing publication bias found that clinical trials with positive findings were nearly four times more likely to be published than trials with negative findings.²⁸ Furthermore, trials with positive findings tended to be published sooner—after four to five years—than those with negative findings, which were published after six to eight years.

Publishing Data from Phase 2 Clinical Trials Without Confirmatory Data from Phase 3 Trials — Under the FDA’s existing guidance for industry on good reprint practices, pharmaceutical and medical device manufacturers may promote drugs and devices for unapproved uses by distributing reprints of medical journal articles that present results of phase 2 clinical trials that tested medical products for such uses even if phase 3 trials related to those uses have not been conducted or completed. As the agency is well aware, however, results of phase 2 clinical trials can provide misleading information about the safety and effectiveness of products.

The FDA highlighted this point in its recent report describing 22 carefully documented case studies of drugs, vaccines, and medical devices for which promising phase 2 clinical trial results were not confirmed in phase 3 trials.²⁹ The agency’s analysis of these cases revealed that phase 3 results did not confirm effectiveness in 14 cases, did not confirm safety in one case, and failed to confirm both safety and effectiveness in seven cases.³⁰ Six cases involved prescription

²⁶ Prasad V, Berger V. Hard-wired bias: How even double-blind, randomized controlled trials can be skewed from the start. *Mayo Clin Proc.* 2015;90(9):1171-1175.

²⁷ *Id.*

²⁸ Hopewell S, Loudon K, Clarke MJ, et al. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database of Systematic Reviews.* 2009, Issue 1. Art. No.: MR000006. DOI:10.1002/14651858.MR000006.pub3.

²⁹ FDA. 22 Case Studies Where Phase 2 and Phase 3 Trials Had Divergent Results. Available at <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM535780.pdf>. [Last accessed Feb. 27, 2017] at 2.

³⁰ *See id.*

drugs that were already approved by the FDA for one use but undergoing clinical testing for another use.³¹ The selected cases were “chosen from a large pool of similar examples.”³² The FDA noted the following:

These unexpected results [from phase 3 trials] could occur even when the phase 2 study was relatively large and even when the phase 2 trials assessed clinical outcomes. In two cases, the phase 3 studies showed that the experimental product increased the frequency of the problem it was intended to prevent.³³

The agency concluded the following:

[T]he 22 cases explored in this paper demonstrate that phase 2 results can inaccurately predict safety and/or effectiveness for medical products in a wide range of diseases and patient populations. These cases also help illustrate the potential public health implications of undue reliance on phase 2 studies and the benefits of conducting Phase [3] studies. As a result of the Phase [3] studies discussed in this paper, patients outside of clinical trials were not subjected to drugs that would not benefit them or to the risk of unnecessary serious toxicities, and did not suffer unnecessary financial expenditures. Where effective alternative therapies existed, they were not diverted from proven treatments; where an implanted medical device was at issue, patients were spared unnecessary surgical procedures.³⁴

The FDA’s recent report thus demonstrates the risks of allowing promotion of uses before successful completion of phase 3 studies and subsequent review and approval by the FDA. Until that point, physicians and patients cannot be reasonably assured of the safety and effectiveness of the product.

Selective Reporting in Educational Materials and Published Articles — Allowing distribution of peer-reviewed literature about unapproved uses also skews physicians’ perceptions of the safety and effectiveness of those uses because, as has been well documented, manufacturers selectively report study findings that are most favorable for their products. When selecting educational material to send to doctors or to present at seminars, manufacturers choose material that plays up positive results and omits information about side effects, adverse reactions, and warnings.^{35,36} For example, studies comparing information in documents submitted to the FDA for approval of a drug^{37,38} or high-risk medical device³⁹ with information reported in peer-

³¹ See *id.* at 34.

³² *Id.* at 2.

³³ *Id.*

³⁴ *Id.* at 29-30.

³⁵ *Washington Legal Foundation v. Friedman*, 13 F. Supp. 2d 51 (D.D.C. 1998), *vacated on other grounds*, 202 F.3d 331 (D.C. Cir. 2000).

³⁶ Ford M. Another use of OxyContin: The case for enhancing liability for off-label drug marketing. *BU L Rev.* 2003;83:429-464.

³⁷ Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: Review of publication and presentation. *PLoS Med.* 2008;5(11): e217. DOI:10.1371/journal.pmed.0050217. (Correction: *PLoS Med* 6(1): e1000017. doi:10.1371/journal.pmed.1000017)

reviewed medical journal articles have revealed frequent discrepancies in identified primary endpoints and primary study results. Likewise, another study found that drug companies selectively report the outcomes of clinical trials.⁴⁰ Unsurprisingly, the studies drug companies choose not to publish overwhelmingly report negative or inconclusive results.⁴¹ In 2004, for example, Merck withdrew Vioxx from the market after revelations emerged that the company had suppressed evidence that the drug caused an increased risk of heart attack and that the company had attempted to discredit or “neutralize” doctors who were critical of the drug.⁴²

The FDA itself, in its 2010 Transparency Task Force report, noted, “Selective publication of clinical trials results has, in the past, created a misleading picture of the safety and efficacy of a product, with negative implications for the public health. This is particularly pronounced when the product is used off-label.”⁴³

Ghostwriting — The problem of inherent bias in the reported studies is exacerbated when companies hire ghostwriters or recruit academics to pose as authors.⁴⁴ For example, Parke-Davis designed and commissioned research to promote its drug Neurontin and devised a “publication strategy” that included contracts with medical education companies to write articles on specified topics involving off-label use.⁴⁵

In sum, restrictions on marketing drugs and devices for unapproved uses are crucial because reliance on publication of a study is no substitute for the FDA’s rigorous, independent evaluation of the evidence. “FDA assigns review teams and primary reviewers who specialize in that scientific discipline to review that portion of the application and to generate a written evaluation. FDA then integrates the conclusions from these separate review activities to

³⁸ Turner EH, Knoepflmacher D, Shapley L. Publication bias in antipsychotic trials: An analysis of efficacy comparing the published literature to the US Food and Drug Administration database. *PLoS Med.* 2012;9(3): e1001189. DOI:10.1371/journal.pmed.1001189.

³⁹ Chang L, Dhruva SS, Chu J, et al. Selective reporting in trials of high risk cardiovascular devices: Cross sectional comparison between premarket approval summaries and published reports. *BMJ.* 2015 June 10;350:h2613.

⁴⁰ Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use. *New Engl J Med.* 2009;361:1963–1971.

⁴¹ Turner EH, Matthews AM, Linardatos E, et al. Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy. *New Engl J Med.* 2008;358:252–260.

⁴² Walters C. Researchers Reveal Merck’s Ghostwritten Vioxx Studies. *Trial.* July 2008.

⁴³ Food and Drug Administration Transparency Task Force. FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration. May 2010. Available at <http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212110.pdf>. [Last accessed Nov. 6, 2016]

⁴⁴ Ross J, Hill KP, Egilman DS, Krumholz HM. Guest Authorship and Ghostwriting in Publications Related to Rofecoxib. *JAMA.* 2008;1800–1812.

⁴⁵ See Landefeld S, Michael A, Steinman M. The Neurontin Legacy—Marketing through Misinformation and Manipulation. *New Engl J Med.* 2009;360:103–106 (Parke-Davis engaged in ‘the systematic use of deception and misinformation to create a biased evidence base and manipulate physicians’ beliefs and prescribing behaviors.’).

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determine the appropriate outcome for the application.”⁴⁶ The agency is correct that its “multi-disciplinary scientific review cannot be replicated by individual health care providers.”⁴⁷

As Avorn and colleagues aptly explained in their 2015 *New England Journal of Medicine* article, “physicians and patients could not be expected to determine whether a given drug was safe and effective without having the benefit of the lengthy and complex evaluation process conducted by FDA scientists and its outside advisors, who assess reams of complex data on pharmacology and clinical trial results, not all of which are publicly available.”⁴⁸ Public Citizen believes that stronger restrictions would better protect patients and urges the agency to strengthen its efforts to block promotion of drugs and medical devices for unapproved uses.

THE FIRST AMENDMENT

As the FDA is well aware, the pharmaceutical and medical device industries invoke the First Amendment to support their push to engage in increased promotion for unapproved uses. In our view, the First Amendment provides strong support for the existing regulatory regime and restrictions.

The pharmaceutical industry—most recently the drug company Amarin, supported by other members of the industry as *amici curiae*—has argued that federal laws and regulations providing that prescription drugs can be introduced in commerce only if intended for uses approved by the FDA are a form of content- and speaker-based regulation of speech. That proposition, if accepted, would grant a drug manufacturer the presumptive ability to promote and market a drug for any use once it has received FDA approval for a single use, with the burden on the FDA to prove that the manufacturer’s marketing was deceptive or that the drug was unsafe for that use. But the implications do not stop there. Taken seriously, the proposition that introducing a substance into commerce for a particular purpose is speech fully protected by the First Amendment would imply that, unless it were otherwise unlawful to manufacture or sell a substance, a manufacturer could market that substance as a drug with no approval at all, and its conduct in so doing would receive First Amendment protection unless the government bore the burden of showing that prohibiting the marketing of the drug satisfied strict scrutiny. Such a result would overturn the carefully constructed, decades-old regulatory structure that governs pharmaceuticals, which is premised on the FDA’s expertise in determining whether to permit marketing only of drugs that manufacturers have proven to be safe and effective for their intended use.

The heart of the federal regulatory regime governing prescription drugs since the 1962 amendments to the FDCA has been the requirement that manufacturers bear the burden of proving both the safety and effectiveness of their drugs to obtain FDA premarket approval to sell them:

⁴⁶ FDA. Memorandum, *supra* note 13, at 8-9.

⁴⁷ *Id.*

⁴⁸ Avorn J, Sarpatwari A, Kesselheim AS. Forbidden and Permitted Statements about Medications — Loosening the Rules. *N Engl J Med.* 2015;373(10):967-973.

In 1962, Congress amended the FDCA and shifted the burden of proof from the FDA to the manufacturer. Before 1962, the agency had to prove harm to keep a drug out of the market, but the amendments required the manufacturer to demonstrate that its drug was “safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling” before it could distribute the drug. ... In addition, the amendments required the manufacturer to prove the drug’s effectiveness by introducing “substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.”⁴⁹

The interlocking provisions of the FDCA and its implementing regulations establish that if a manufacturer places a drug into commerce with the intent that it be sold for an unapproved use, the manufacturer violates the FDCA’s prohibition on introduction of an unapproved new drug.⁵⁰ Marketing a drug with such intent also violates the prohibition on misbranding a drug, because the drug’s approved labeling will lack adequate directions for the unapproved use.⁵¹

As is generally true of a person’s or company’s intent, the intent with which a drug manufacturer introduces its products into commerce must be inferred, and a pharmaceutical company’s statements in promoting its drugs are a primary source of evidence about its intent.⁵² The industry contends, however, that because it will manifest that intent through commercial speech aimed at encouraging doctors to prescribe products for an unapproved use, its marketing is entitled to First Amendment protection. On this point, the industry often invokes the Second Circuit’s decision in *United States v. Caronia*,⁵³ but the holding of *Caronia* was only that the FDCA does not outlaw promotional speech in and of itself. If it did, the court held, its application to the facts of that case would not have comported with the First Amendment.⁵⁴ The court took care not to hold that using speech to establish a pharmaceutical company’s intent to introduce a drug into commerce for an unapproved use would violate the First Amendment—indeed, it explicitly stated its assumption that “such use of evidence of speech is permissible.”⁵⁵ *Caronia*’s assumption was firmly grounded in the Supreme Court’s holding in *Wisconsin v. Mitchell* that “[t]he First Amendment ... does not prohibit the evidentiary use of speech to establish the elements of a crime or to prove motive or intent.”⁵⁶

⁴⁹ *Wyeth v. Levine*, 555 U.S. 555, 567 (2009) (quoting provisions now codified at 21 U.S.C. § 355(d)).

⁵⁰ 21 U.S.C. §§ 331(d), 355(a).

⁵¹ See *id.* §§ 331(a) & (b), 352(f)(1).

⁵² See *United States v. An Article Consisting of 216 Cartoned Bottles, More or Less*, 409 F.2d 734, 739 (2d Cir. 1969) (“It is well settled that the intended use of a product may be determined from its label, accompanying labeling, promotional material, advertising and any other relevant source.”).

⁵³ 703 F.3d 149 (2d Cir. 2012).

⁵⁴ See *id.* at 161–62.

⁵⁵ *Id.* at 162 n.9. The court further stated that it would be “unclear” whether a manufacturer’s mere knowledge that a doctor intended to put a drug to an unapproved use would establish an illicit intent by the manufacturer in distributing the drug. 703 F.3d at 162 n.9.

⁵⁶ 508 U.S. 476, 489 (1993); see also *United States v. Pierce*, 785 F.3d 832, 841 (2d Cir. 2015); *United States v. Salameh*, 152 F.3d 88, 112 (2d Cir. 1998); *United States v. Kazin*, 559 F. App’x. 32, 35 (2d Cir. 2014).

Even if restrictions on manufacturers' marketing of their products for unapproved uses were properly viewed as speech restrictions, the restrictions would pass muster as reasonable steps to advance the government's substantial interest in protecting and advancing public health by ensuring the safety and effectiveness of drugs and medical devices for each intended use.⁵⁷ This conclusion is bolstered significantly by the fact, discussed above, that so much of manufacturers' promotion for unapproved uses is misleading.

Some manufacturers have argued that the Supreme Court's decisions in *IMS v. Sorrell* and *Reed v. Town of Gilbert* suggest that restrictions on their commercial speech concerning drugs are subject to strict scrutiny under the First Amendment. Those cases, however, are inapposite. First, unlike the FDCA, the state law at issue in *Sorrell*, did not restrict the marketing of a product based on the marketer's intent; it *directly* restrained speech—the dissemination of information.⁵⁸ And *Reed* did not involve commercial speech but a local ordinance that allowed the posting of some temporary signs and barred others based on the content of the signs.⁵⁹

Moreover, even if marketing a drug with the intent that it be put to an unapproved use were subject to First Amendment protection, it would not follow that *Sorrell* or *Reed* would command the application of strict scrutiny. *Sorrell* held that a law that placed content- and speaker-based burdens on pharmaceutical manufacturers' commercial speech was subject to what it called "heightened scrutiny," but the Supreme Court used that term to differentiate the scrutiny applicable in general to "expression protected by the Free Speech Clause of the First Amendment" from the rational-basis scrutiny applicable to non-speech economic regulation, which the state in *Sorrell* advocated.⁶⁰ The Court did not use the term "heightened scrutiny" to specify a particular level of First Amendment scrutiny. To the contrary, the Court declined to determine whether strict scrutiny or the intermediate scrutiny applicable to commercial speech applied to the law at issue because it held that the law could not be upheld under either standard.⁶¹ *Reed*, for its part, said nothing about standards applicable to commercial speech. Subsequently, numerous courts have rejected the argument that *Sorrell* or *Reed* overturned established law that regulations of commercial speech are subject to a lesser standard of justification under the First Amendment than restrictions of non-commercial speech.⁶²

The notion that the use of speech as evidence of someone's intent in distributing a product is not only subject to First Amendment scrutiny, but to strict scrutiny at that, would have broad consequences. Speech is used to discern intent, without First Amendment scrutiny, in a broad range of cases, including, among others, criminal conspiracy, antitrust, and employment

⁵⁷ See *Central Hudson*, 447 U.S. 557 (1980) (setting for standard for restrictions on commercial speech).

⁵⁸ 131 S. Ct. 2653, 2667 (2011).

⁵⁹ 135 S. Ct. 2218 (2015).

⁶⁰ 131 S. Ct. at 2659.

⁶¹ See *id.* at 2667; see also *Caronia*, 703 F.3d at 164 (stating that *Sorrell* "did not decide the level of heightened scrutiny to be applied, that is, strict, intermediate, or some other form of heightened scrutiny").

⁶² See, e.g., *Chiropractors United for Research & Educ., LLC v. Conway*, 2015 WL 5822721, at *5 (W.D. Ky. Oct. 1, 2015); *Contest Promotions, LLC v. City and Cty. of S.F.*, 2015 WL 4571564, at *4 (N.D. Cal. July 28, 2015); *California Outdoor Equity Partners v. City of Corona*, 2015 WL 4163346, at *10 (C.D. Cal. July 9, 2015); *King v. Gen. Info. Servs.*, 903 F. Supp. 2d 303, 307–09 (E.D. Pa. 2012).

discrimination cases. In particular, it is not unusual for a person's intent concerning the commercial use of an item to have consequences with respect to whether his conduct is lawful or unlawful. The Supreme Court, for example, recently considered the federal Controlled Substance Analogue Enforcement Act, which makes unlawful the knowing manufacture or distribution (or possession with intent to distribute) of a substance that is similar in chemical structure and physiological effect to a federally listed controlled substance if the substance is "intended for human consumption."⁶³ The Court held that a conviction under the Act requires that the jury find the defendant possessed knowledge that the substance was an analogue of a controlled substance as well as intent that it be used for human consumption.⁶⁴ Unsurprisingly, the Court's opinion suggests no discomfort with the First Amendment implications of making the defendant's guilt depend on his or her intent with respect to the purchaser's use of the substance.

Under the view of the First Amendment espoused by industry, however, the law would require First Amendment scrutiny if the government sought to prove a defendant's intent based on his or her statements that a buyer could get high if he or she used the analogue. Imposing liability where the defendant had promoted an analogue for such use but not where he or she had sold the substance for use as, say, an engine lubricant would be a "content-based" restriction on speech. And punishing a manufacturer or distributor who had advocated human consumption of a controlled substance analogue, but not a blogger who supported the use of the substance by humans, would, in industry's view, be a "speaker-based" speech regulation. A theory under which the use of speech to prove intent concerning the distribution of controlled substances would be subject to First Amendment scrutiny, let alone strict scrutiny, is dubious, to say the least.

As the FDA has recognized, the industry view of the First Amendment's scope would have extremely broad implications for drug and device regulation because it would call into question the foundation of the regulatory regime.⁶⁵ The regulatory regime is, at its most basic level, triggered by the introduction of a substance into commerce with the intent that it be used to diagnose, cure, mitigate, treat, or prevent disease or to affect the structure or function of the body.⁶⁶ It would, for example, be perfectly legal from the standpoint of the FDCA to introduce a new drug into commerce as an indoor plant food, without FDA review and approval: The FDCA would not classify the substance as a drug if sold with the intent that it be used in that manner, and, hence, it would not require FDA approval. The industry's First Amendment theory, however, suggests that if a manufacturer could lawfully market the substance for that non-drug use but could not, without approval, lawfully market it for use to prevent disease, the imposition of criminal or civil liability on the manufacturer for selling the product as a drug without

⁶³ *McFadden v. United States*, __ U.S. __, 2015 WL 2473377, at *4 (2015) (discussing 21 U.S.C. § 813).

⁶⁴ See *id.* at *5.

⁶⁵ *Amarin Pharma Inc. v United States Food & Drug Administration*, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015) (quoting FDA brief and FDA statement at oral argument).

⁶⁶ See *216 Cartoned Bottles*, 409 F.2d at 739 ("Regardless of the actual physical effect of a product, it will be deemed a drug for purposes of the Act where the labeling and promotional claims show intended uses that bring it within the drug definition."); see also, e.g., *Whitaker v. Thompson*, 353 F.3d 947, 949–52 (D.C. Cir. 2004); *United States v. Cole*, __ F.3d __, 2015 WL 471594, at *3 (D. Or. Feb. 5, 2015); *United States v. Livdahl*, 459 F. Supp. 2d 1255, 1259–60 (S.D. Fla. 2005).

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approval would require First Amendment scrutiny because liability would be based on the manufacturer's speech in promoting the product as a drug.⁶⁷ Moreover, according to some industry arguments, the prohibition on selling an unapproved drug as a drug rather than as fertilizer would be subject to strict scrutiny, under which, they argue, the burden would be on the FDA to prove that the unapproved substance posed dangers that were sufficient to create a compelling interest in stopping the manufacturer from marketing it as a drug.

Assertions that the FDCA's fundamental requirement of premarket approval violates the First Amendment because it is based on an inference of intent from the manner in which a manufacturer markets a product have, when made directly, been rejected by the courts.⁶⁸ The FDA should not allow expanded promotion for unapproved uses based on that argument. Such expansion is not constitutionally required and would be detrimental to important protections for public health and safety. The FDCA's requirement that manufacturers bear the burden of proving both the safety and effectiveness of new drugs for their intended uses is *critical* to achieving Congress's objectives of protecting the public against unsafe or worthless pharmaceutical products.

Last year, the judge presiding over the *Amarin Pharma* litigation suggested that the current drug-approval framework may be inconsistent with "modern First Amendment law."⁶⁹ That judge's worrisome suggestion is not correct. The First Amendment provides no protection to commercial speech—speech that proposes a commercial transaction—if that speech is false or misleading. And messages promoting unapproved uses are necessarily misleading when they suggest a health benefit that has not been established. Even beyond the misleading nature of much off-label promotion, the First Amendment is no bar to commercial speech restrictions that advance substantial government interests. The FDCA regulatory scheme, and in particular the drug-approval process, was developed over the 20th Century to protect a very substantial government interest: protecting public health. The First Amendment view set forth in the *Amarin* decision fails to understand the balancing that is at the very heart of First Amendment cases and the invaluable role of the regulatory scheme in protecting patients from unsafe or ineffective drugs.

CONCLUSION

History shows that after-the-fact enforcement is inadequate to protect patient safety. Rather, when an unproven assertion of safety and effectiveness is relied on, the resulting harm may be severe—even, as was the case with Elixir Sulfanilamide, irreparable. In the strongest

⁶⁷ Cf. *Caronia*, 703 F.3d at 180 (Livingston, J., dissenting).

⁶⁸ See *Whitaker*, 353 F.3d at 953; *United States v. Cole*, 2015 WL 471594, at *4–5; see also *Holistic Candlers & Consumer Ass'n v. FDA*, 770 F. Supp. 2d 156, 164 & n.15 (D.D.C. 2011) (characterizing First Amendment challenge to requirement of premarket approval for medical device as "foreclosed by settled law holding that use of speech to establish an element of a violation does not violate the First Amendment"), *aff'd on other grounds*, 664 F.3d 940 (D.C. Cir. 2012).

⁶⁹ *Amarin Pharma Inc. v. United States Food & Drug Administration*, 119 F. Supp. 3d at 226.

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terms, we urge the FDA to strengthen, not loosen, its restrictions on promotion of drugs and medical devices for unapproved uses.



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Testimony Submitted for the Record

**U.S. House Energy and Commerce Committee
Subcommittee on Health**

Hearing on “Examining Medical Product Manufacturer Communications”

**John Rother
Executive Director**

The Campaign for Sustainable Rx Pricing (CSRxP)

July 12, 2017

Chairman Burgess, Ranking Member Green, and members of the House Energy and Commerce Subcommittee on Health, the Campaign for Sustainable Rx Pricing (CSRxP) thanks you for the opportunity to submit testimony for the record on medical product manufacturer communications.

CSRxP is a project of the National Coalition on Health Care Action Fund. We are a broad-based coalition of leaders – physicians, nurses, hospitals, consumers, health plans, PBMs, pharmacists, and businesses – promoting bipartisan, market-based solutions to lower drug prices in America. It is a fact: prescription drug prices are out of control. The consequences of this crisis hurt everyone, from patients and consumers to doctors, hospitals, and hardworking taxpayers. That’s why it is critical to solve this crisis now with smart, effective solutions that work.

CSRxP believes that permitting more open medical product manufacturer communications will provide increased certainty and clarity to payers as they predict and prepare for future spending on emerging therapies, thus allowing them to set more stable premium and out-of-pocket spending levels for consumers over time. Such communications should have appropriate parameters, however, so that manufacturers maintain incentives to undergo the FDA approval process, thereby giving U.S. patients, their families, and their healthcare providers peace of mind that the products they use are safe and effective.

H.R. 2026, the Pharmaceutical Information Exchange Act would facilitate more open, pre-decisional communication – communication about an emerging therapy prior to FDA approval or clearance – between manufacturers and payers while at the same time preserving appropriate incentives for manufacturers to seek FDA approval for their products. With respect to H.R. 1703, the Medical Product Communications Act of 2017, CSRxP believes Congressional action may be premature and warrant further consideration of the issues as presented in the legislation.

I. Pre-decisional manufacturer communications can help payers establish more predictable rates for patients and consumers over time, as well as enable more use of value-based payment arrangements.

Healthcare stakeholders try to forecast costs of healthcare spending several years into the future to keep rates and premiums as predictable as possible for patients and their families. Predictability results in more stable rates and fewer unexpected spikes in year-over-year out-of-pocket costs and premiums – a particularly meaningful benefit to U.S. consumers as they consider their healthcare needs.

Accurate rate development relies on detailed assumptions about the anticipated utilization of health care services, including prescription drugs and medical devices. Without accurate, reliable, and more transparent clinical and pharmacoeconomic information about new products or expanded indications of existing products, payers cannot appropriately account for emerging therapies when budgeting for the future – whether it be for a hospital system or for a health plan setting premiums. The concern is becoming more acute as medical products are moving more quickly and efficiently through the FDA approval process.

Moreover, more open and transparent pre-decisional communications may better position payers to conduct their own population-based value assessments of therapies and related benefit designs to broaden use of value-based healthcare payment strategies. For example, such information could support development of outcome-based contracts and indications-based pricing arrangements.

II. Drug makers should be able to engage in more transparent pre-decisional communications about their products only if they also are required to be more transparent in their drug pricing strategies prior to FDA approval.

More open communications should be considered just the first step in the broader goal of creating more transparency into how pharmaceutical companies determine how they are going to price their products. Without requiring the pharmaceutical industry to be more transparent on drug pricing and price growth, American patients and their families will continue to face unsustainable and needless increases in prescription drug costs.

Consequently, CSRxP strongly urges that any legislation which permits drug makers to conduct more open and transparent pre-decisional communications about their products also must require them to be more transparent about product pricing prior to FDA approval. Such information should include the maximum unit price the drug maker intends to charge for the product; the cost of a course of treatment; the label under discussion with the FDA that indicates the target population with other important clinical details; and a projection of federal spending on the product.

More transparent pre-decisional drug pricing also could help payers expand use of value-based healthcare payment strategies, which potentially can lower costs, increase access and improve health outcomes for patients taking these medications. In other words, pre-approval drug pricing transparency is a critical strategy in making prescription drugs more affordable for all Americans, while at the same time, maintaining and potentially expanding access to treatments that can improve patient health and quality of life.

III. Communications should follow a regulatory framework that enables manufacturers to convey pre-decisional information about their products while at the same time ensuring that incentives remain to have the products go through the FDA approval process.

Knowing that medical products are safe and effective for use is critical for both patients and the prescribing physicians. Hence, any pre-decisional manufacturer communications should maintain appropriate safeguards to incentivize manufacturers to go through the FDA approval process, which deems their products safe and effective for patient use. Such safeguards should include the following:

- Pre-decisional communications only should reflect scientifically-sound, competent and reliable evidence that is truthful, non-misleading, and unbiased. The communications should include information such as risk/benefit and quality data, as well as appropriate disclaimers on the limitations of the data presented.
- Existing FDA policies should not be modified in any way that would extend increased flexibility to manufacturers to promote off-label uses of their products directly to consumers. Rather, pre-decisional communications only should occur between entities with both financial and clinical interests in avoiding the unintended consequence of affecting prescribing practices by physicians directly treating patients. For example, any communications between manufacturers and medical service providers should adhere to specific criteria to ensure the information is relevant, scientifically sound and responsibly presented. They should be limited to appropriate proactive requests to manufacturers or to certain venues that meet widely accepted and recognized standards for communications about scientific and clinical data such as scientific journals, clinical practice guidelines, and compendia, but not to lay media, letters to the editor, or proactive and reactive communications.
- Manufacturers only should discuss information related to medical product indications undergoing FDA review.
- The pre-decisional communications only should occur within a certain timeframe of the expected FDA approval date.

- Given the many emerging technologies and evolving organizations and relationships into which manufacturers enter, the FDA should have latitude to periodically revisit and reassess the definitions of entities covered by the pre-decisional communications safeguards.

The FDA currently is reviewing the extent to which appropriate safeguards, such as those outlined above, may allow for additional communications from manufacturers about their products. As noted above, with respect to H.R. 1703, CSRxP believes the FDA should complete its review prior to any Congressional action to expand the definition of scientific exchange between manufacturers and health care professionals so that any expanded communications strictly include information that is truthful, non-misleading, unbiased, supported by competent and reliable evidence, relevant, and responsibly presented.

IV. Conclusion

CSRxP appreciates the Subcommittee's leadership and, again, thanks the Subcommittee for the opportunity to submit testimony for the record on medical product manufacturer communications. We look forward to collaboration in the future on developing market-based policies that promote competition, transparency, and value to make prescription drugs more affordable for all American patients and their families while at the same time maintaining access to the treatments that can improve health outcomes and save lives.



STATEMENT FOR THE RECORD

**Submitted to the
House Energy and Commerce Committee
Subcommittee on Health**

Examining Medical Product Manufacturer Communications

July 12, 2017

America's Health Insurance Plans
601 Pennsylvania Avenue, NW
Suite 500, South Building
Washington, D.C. 20004

America's Health Insurance Plans (AHIP) is the national association whose members provide coverage for health care and related services to millions of Americans every day. Through these offerings, we improve and protect the health and financial security of consumers, families, businesses, communities and the nation. We are committed to market-based solutions and public-private partnerships that improve affordability, value, access and well-being for consumers.

We appreciate this opportunity to offer our comments on two draft bills addressing pharmaceutical manufacturer communications on medical products: the "Medical Product Communications Act" and the "Pharmaceutical Information Exchange Act." Proposed changes to the rules surrounding these communications could have far-reaching implications for the decisions made by health care providers, in consultation with their patients, about which medications and other medical products are safe, effective, and appropriate for treating their patients. We believe it is critically important for Congress to fully consider the potential impact of these proposed changes on patient safety, health outcomes, and our shared goal of promoting high quality, affordable health care for all Americans.

"Medical Product Communications Act" (H.R. 1703)

Patients deserve to have more information about their medical care -- from the cost of their care, to the quality of their providers, to the efficacy of their treatments. With more information, more consumers can make better-informed decisions. However, it is critical to understand that better decisions are based on *accurate, evidence-based* information -- not just *more* information. Information that is inaccurate, incomplete, or inconclusive helps no one.

Health insurance providers are committed to helping every patient access high-quality care that gets them well when they're sick and keeps them well when they're healthy. That means finding the safest, most effective treatments that best meet the individual needs of individual patients. That may include the innovative use of prescription drugs for conditions that are not specifically approved by the Food and Drug Administration (FDA) and not included or indicated on the product label. This "off-label" use has helped many patients get well and stay healthy. When there is strong evidence to support off-label use of prescriptions drugs, health plans often provide coverage for such usage. For example, in the Medicare prescription drug program, Part D plans

cover drugs prescribed for off-label use if the drugs are identified as safe and effective for that use in certain officially recognized drug compendia.¹

The “Medical Product Communications Act” would not provide or ensure that patients and care providers have access to better research and evidence. Rather, it would allow drug manufacturers to communicate information about prescription drugs that has not been approved by the FDA. The lack of approval may be due to contradictory evidence – or the lack of any evidence at all – or the need for additional research.

The FDA’s current requirements for meeting high standards of evidence for safety and efficacy help ensure that robust evidence exists to support approval of drugs, biologics, and devices for specific uses and indications. To truly help patients get the most effective treatments, it is essential to maintain the highest standards of safety, research and evidence. These rules – and the incentives for manufacturers to comply with proper FDA processes – should be preserved.

Because we want to ensure that patients and care providers have access to accurate information based on the best possible research and the strongest possible evidence, AHIP does not support this legislation. We have serious concerns that it could undermine the FDA’s efforts to ensure that providers and patients receive information that is truthful, is supported by rigorous scientific evidence, and is not misleading or biased. Specifically, we are concerned that allowing drug manufacturers to communicate about unapproved uses of their products reduces the incentive for them to go through the FDA’s supplemental application approval process. The draft legislation proposes removing the scientific exchange of off-label uses from the definition of “intended use” of the drug or device, preventing the FDA from any oversight of the scientific exchange of information about off-label uses of drugs and devices. This, in turn, reduces the incentive for manufacturers to conduct large, well-controlled, randomized clinical trials that would prove a product is both safe and effective for a particular indicated use.

Ultimately, this result would weaken the FDA’s role to ensure patient safety and public health, introducing far more safety risks into the health care system than potential rewards.

Additionally, at a time when policymakers are working on ways to increase value and decrease

¹ Social Security Act §1860D-2(e)(4)(A). Also of note, drugs indicated to treat sexual or erectile dysfunction are not covered in Medicare Part D, and coverage of any off-label uses of such indicated drugs are also prohibited under Social Security Act §1860D-2(e)(2)(A).

costs across the health care system, we must consider that this has the potential to dramatically increase costs by utilizing potentially expensive therapies, without substantial evidence of better care, better quality, or better outcomes.

We also want to emphasize that – even without the proposed legislation – health care service providers already have access to scientific information about unapproved uses of medical products, and physicians currently are free to use drugs for “off-label” indications. This information is widely available through public sources such as scientific journals, clinical practice guidelines, and compendia.

While these existing sources of information provide evidence-based information with respect to the safety and efficacy of medical products, a recent *Journal of the American Medical Association* (JAMA) study tracking off-label use in 45,000 adults through electronic health records (EHRs) over 2005-2009 found that, of the off-label prescriptions studied, 80 percent lacked scientific evidence and had a higher occurrence of adverse drug events (ADEs). The study concluded that off-label use is associated with a higher occurrence of ADEs, and recommended that EHRs “be designed to enable postmarketing surveillance of treatment indications and treatment outcomes to monitor the safety of on- and off-label uses of drugs.”²

We appreciate that the parameters around the scientific exchange of off-label uses have been strengthened in the draft legislation, preventing the communications from promotional use and requiring competent and reliable scientific evidence and appropriate contextual information regarding any limitations of evidence. However, we believe these communications would be inherently promotional and less likely to reflect the rigorous scientific analysis that providers need to serve the best interests of their patients while preventing adverse events.

The FDA currently is reviewing its policies to determine the extent to which additional communications from manufacturers can provide access to information on off-label uses that is relevant, scientifically sound, and responsibly presented. We believe this process offers promise for developing a common sense policy. AHIP has submitted comments to the FDA, urging the agency to consider defining allowable parameters for these communications, such as limiting

² Tewodros Equale, et al., “Association of Off-label Drug Use and Adverse Drug Events in an Adult Population,” *Journal of the American Medical Association Internal Medicine* 176, no. 1 (2016): 55-63, doi:10.1001/jamainternmed.2015.6058.

them to indications undergoing FDA review and occurring within a certain timeframe of the expected FDA approval date. We also recommend that the communications include risk-benefit and quality data, appropriate disclaimers (including the limitations of such evidence), and other relevant information.³

We appreciate the committee's interest in examining the rules that apply to manufacturer communications on "off-label" uses, as many of these issues have been the subject of legal disputes. However, we urge you to proceed cautiously when considering the pending draft legislation and take into consideration the long-term patient safety implications, the potential increase in health care costs associated with investigational drug use, and the FDA's deliberations on this issue.

"Pharmaceutical Information Exchange Act" (H.R. 2026)

The "Pharmaceutical Information Exchange Act" would expand the ability of drug and device manufacturers to share health care economic information (HCEI) and scientific information with payors, formulary and technology review committees, and similar entities for investigational use drugs and devices before they are approved by the FDA.

We addressed these issues in a comment letter we recently submitted to the FDA.⁴ Our letter highlighted our members' priorities in three areas:

- The importance of holding communications between manufacturers and payers, formulary committees, and similar entities to strong evidentiary standards;
- The value of a regulatory framework that enables manufacturers to communicate HCEI or real world evidence (RWE) related to an FDA-approved indication to payers, formulary committees, and similar entities; and,

³ AHIP [letter](#) to Food and Drug Administration, responding to request for comments on "Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products." April 18, 2017.

⁴ AHIP [letter](#) to Food and Drug Administration, providing comments on draft guidance on "Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities -- Questions and Answers." April 18, 2017.

- The need for timely and appropriate communications based on strong evidentiary standards between manufacturers and payers, formulary committees, and similar entities about products that are investigational or under review by the FDA.

AHIP supports the goals of this draft legislation. The current uncertainty over what communications are permitted often makes it difficult for health plans to obtain reliable HCEI related to an FDA-approved indication and therefore complicates their efforts to make accurate assessments regarding value, pricing, and utilization. Health plans need sound information based on strong evidentiary standards to inform estimates of anticipated costs for up to several years into the future when making business decisions involving pricing and contracts.

In addition, because this information is not permitted for products that are labeled investigational or under FDA review, it is currently difficult for plans to obtain information about manufacturer pipelines (including both new products and additional indications for existing FDA-approved products), which is also essential to their ability to make accurate assessments about value, pricing, and utilization in the longer term. A regulatory framework that enables manufacturers to communicate with payers regarding products that are investigational and under review by the FDA will allow payers to take that information into consideration as they plan for and make coverage and reimbursement policies far in advance of the effective date of the decisions. Additionally, early and appropriate communication of this type of information can enable manufacturers and payers to develop alternative, value-based payment arrangements, such as outcome-based contracts and indication-specific pricing.

While we support the goals of this draft legislation, we would like to reemphasize the importance of ensuring these communications promote patient safety and public health. Safeguards must be in place so that information communicated regarding HCEI for products that are investigational or under review be held to strong evidentiary standards. We appreciate that the draft legislation requires these communications to be based on “competent and reliable scientific evidence” (CARSE), and support the FDA’s intent to consider HCEI to be based on CARSE if “the HCEI has been developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results.”

Additionally, we believe the FDA should periodically revisit and reassess the definitions and entities covered. Over time, emerging technology, evolving organizations and relationships,

along with other changes in health care may create some ambiguity in the intended audience for these communications. It will be important to ensure that the information sharing occurs between sophisticated entities with both a financial and clinical interest to avoid the unintended consequence of affecting prescribing practices by physicians who are directly treating patients.

Thank you for considering our views on these draft bills. We stand ready to work with you on medical product manufacturer communications. We also look forward to working with you on broader issues surrounding the high cost of prescription drugs and the need for market-based solutions to ensure that consumers have access to affordable medications.

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS
Congress of the United States
House of Representatives
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August 17, 2017

Ms. Coleen Klasmeier
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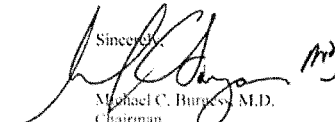
Dear Ms. Klasmeier:

Thank you for appearing before the Committee on Energy and Commerce on July 12, 2017, to testify at the hearing entitled "Examining Bipartisan Legislation to Improve the Medicare Program."

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.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on August 31, 2017. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Committee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

Responses to Additional Questions for the Record

The Honorable Michael C. Burgess

1. We heard testimony as to the need for FDA to act as a “learned intermediary” between manufacturers and prescribers with respect to scientific information disseminated under the proposed legislation. Would it represent a significant shift in federal medical product regulation if the law were to require all manufacturer communications to be reviewed by FDA in advance? What is the scope of FDA’s authority under current law to substitute its judgment for that of a prescriber when it comes to drug and medical device use?

Requiring prior FDA review of all manufacturer communications would represent a significant shift in federal medical product regulation, because Congress has expressly limited FDA’s authority to require prior agency review of manufacturer communications. Under Section 502(n) and (r) of the Federal Food, Drug, and Cosmetic Act (FDCA), “except in extraordinary circumstances, no regulation issued under this paragraph shall require prior approval by the Secretary of the content of any [prescription drug or restricted device] advertisement[.]”¹ If the law were changed to require prior FDA review of all manufacturer communications, then FDA would be unable to maintain its well-established policy of permitting manufacturers to engage in certain communications with respect to new uses of lawfully marketed medical products. A new requirement of prior FDA approval would also raise constitutional issues.

Congress did not give FDA the power to regulate all manufacturer speech. The FDCA authorizes FDA to regulate the content of prescription drug and restricted device “labeling” and “advertising.”² Manufacturer communications outside the scope of the relevant statutory provisions are not subject to regulation by FDA. In addition, although FDA requires manufacturers to substantiate efficacy claims prior to marketing through the new drug and device clearance and approval processes, FDA rules have long permitted manufacturers to promote their products using accurate, substantiated claims about clinical benefits, price, and other product attributes, all without prior authorization and without requiring that the claims be derived from approved labeling.³

Nor does FDA regulate “scientific information” about drugs and medical devices, except to the extent such information qualifies as “labeling” or “advertising” as discussed above. FDA has determined, as a matter of policy, that manufacturers should have the ability to provide scientific information to practitioners, payors, and patients about drugs and medical devices, including investigational products

¹ 21 U.S.C. § 352(n), (r). See also 21 C.F.R. §§ 202.1(j)(1)-(3), 314.550. In rare instances, FDA prior approval of promotional materials has been a component of a negotiated resolution of an enforcement action or investigation.

² 21 U.S.C. §§ 321(n), 352(a), (f)(1), (n), and (r). FDA is also authorized to regulate oral statements by sales representatives indirectly, on the ground that such statements create new “intended uses” for lawfully marketed products. See 21 C.F.R. §§ 201.128, 801.4.

³ E.g., 21 C.F.R. §§ 200.200, 202.1(e)(2)(i) & (6)(i).

and new uses of lawfully marketed products, without those communications triggering FDA regulation. FDA's policy is reflected in numerous agency statements, including regulations and guidance documents, facilitating manufacturer "scientific exchange," manufacturer dissemination of journal article reprints and other publications that include information regarding new uses of medical products, manufacturer responses to unsolicited requests, and manufacturer support for continuing education and similar events at which new uses will be discussed. FDA's policy is one of "delicate balance" between enforcement of the FDCA and support for patient care through manufacturer communication of useful information to facilitate health care practitioner decisions with respect to the uses of drugs and medical devices.⁴

Once FDA has authorized marketing, the agency generally lacks the authority "to substitute its judgment for that of a prescriber" with respect to the use of that product. The FDCA is not a broad grant of power with respect to health care delivery or medical or surgical practice. Congress intended for FDA to influence medical practice only indirectly, by applying the statutory provisions governing the market introduction of new drugs and medical devices and the related provisions governing the content of labeling.⁵ As FDA explained more than four decades ago:

[A]lthough it is clear that Congress did not intend the Food and Drug Administration to regulate or interfere with the practice of medicine, it is equally clear that it did intend that the Food and Drug Administration determine those drugs for which there exists substantial evidence of safety and effectiveness and thus will be available for prescribing by the medical profession, and additionally, what information about the drugs constitutes truthful, accurate, and full disclosure to permit safe and effective prescription by the physician. As the law now stands, therefore, the Food and Drug Administration is charged with the responsibility for judging the safety and effectiveness of drugs and the truthfulness of their labeling. The physician is then responsible for making the final judgment as to which, if, any, of the available drugs his patient will receive in the light of the information contained in their labeling and other adequate scientific data available to him.⁶

⁴ 59 Fed. Reg. 59,820, 59,825 (Nov. 18, 1994). *See also* 61 Fed. Reg. 52,800, 52,800 (Oct. 8, 1996); 57 Fed. Reg. 56,412, 56,412 (1992).

⁵ In addition to reviewing and approving the official product labeling for a drug or medical device, FDA has the opportunity to review and provide comments on promotional labeling and advertising for prescription drugs when those materials are submitted to the Office of Prescription Drug Promotion (OPDP) within the Center for Drug Evaluation and Research (CDER) in accordance with 21 C.F.R. § 314.81(b)(3)(i). Manufacturers also commonly submit proposed promotional materials to OPDP for prior review incident to launch, and consumer-directed television advertisements are routinely submitted for prior review by OPDP in accordance with industry guidelines.

⁶ 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972). *See also* 21 U.S.C. § 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale

In certain cases, FDA may impose specific restrictions on the use of a product in order to mitigate serious risks, such as requirements that prescribers of a drug have particular training, experience, or certification. Congress has authorized FDA to restrict the uses of a medical product by prohibiting the use of human growth hormone for uses not approved by the Agency.⁷ In all other cases, prescribers employ their own medical judgment in determining the appropriate uses of medical products.

A change in federal law to require prior FDA approval of all manufacturer communications would raise significant constitutional concerns. As the Supreme Court has recognized, the First Amendment protects truthful and non-misleading speech by medical product manufacturers, including commercial speech comprising “labeling” and “advertising.” Moreover, the government may not restrict accurate speech about lawful activity (including off-label use) in order to prevent “bad decisions” or to influence health care practitioners or patients to make choices the government prefers.

or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.”).

⁷ 21 U.S.C. § 353(e). Product use is also limited by prescription-only designation (including restricted designation for medical devices).

2. We heard testimony regarding the inability of any manufacturer to provide complete information about a new use. It was also suggested that FDA is the only source of complete information about the full range of medical product uses. What information does FDA receive from manufacturers, adverse event reporting, and other sources, and how does that information compare to the data and analysis to which the manufacturer has access?

In general, FDA will not have “complete” information about all uses of a medical product. Manufacturers often have unique access to information about their products, including new uses.⁸ FDA has acknowledged for many years, and recently reaffirmed, that “[s]cientific departments within regulated companies generally maintain a large body of information on their products.”⁹ FDA generally relies on manufacturers to provide the agency with information about their products, such as adverse events and other product information subject to reporting by manufacturers under the FDCA. This includes information about off-label uses. For example, FDA requires manufacturers to review and analyze information about adverse events associated with their products, including events that involve an off-label use.¹⁰

In recent years, FDA has sought to supplement the current regulatory scheme driven by manufacturer reporting with national systems for active identification of new risks associated with approved products, including Sentinel and the National Evaluation System for Health Technology (NEST). The regulatory scheme is nonetheless largely designed to require the manufacturer to collect and analyze information in the first instance, thereby enabling FDA to allocate finite resources effectively by focusing on issues and categories of information that are most likely to have public health impact. For example, FDA does not require manufacturers to inform the agency of every published study about a product. Rather, the manufacturer is required to notify FDA on an expedited basis if such a study describes a serious adverse event.¹¹

⁸ *Wyeth v. Levine*, 555 U.S. 555, 578-79 (2009) (“manufacturers have superior access to information about their drugs”).

⁹ 59 Fed. Reg. 59,820, 59,823 (1994); FDA, Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices 2 (Dec. 2011).

¹⁰ 21 C.F.R. § 314.80(b)-(c).

¹¹ *E.g.*, 21 C.F.R. § 314.80(d).

3. It has been suggested that off-label information might be more useful in some areas of practice than in others. How should the subcommittee evaluate that issue, and is there a principled basis in the law for making a distinction in the regulation of information dissemination according to the nature of the disease area (e.g., rare diseases, oncology) or patient population (e.g., pediatrics)?

Off-label use is particularly prevalent in certain patient populations and disease areas. These include:

- Pediatrics, where most drugs simply have no information in approved labeling addressing use in children. This is a particular issue for preterm infants, newborns, young children, and children with chronic or rare diseases.
- Oncology, where off-label use is a mainstay and satisfies critical, unmet patient needs. Because of the high morbidity and mortality observed in many cancer patients, oncologists quickly incorporate into clinical practice emerging data regarding potentially effective new uses.
- Psychiatry, where multiple treatment attempts and methods may be necessary before a successful therapy can be found for a patient, and a drug that is approved to treat one condition may also treat a related, but unlabeled, one. Psychiatric patients are treated based on symptoms rather than on specific diagnoses, and there are even psychiatric disorders for which no approved drug has an indication, such that off-label use is the only option for drug therapy. Even if FDA has approved a drug for a particular condition, the patient may fall outside the labeled patient population, or might need a higher or lower dosage.
- Rare diseases, where many patients are prescribed at least one drug for an off-label use.¹²

Legally, however, there is no basis on which to regulate all information dissemination according to disease area or patient population. The FDCA simply does not authorize FDA to regulate speech on that basis. And, although the case law is extensive and complex, a basic First Amendment principle prohibits a government agency from forbidding truthful, non-misleading speech about lawful activity, and off-label use remains lawful and appropriate (and indeed may constitute the standard of care) across many therapeutic scenarios. As a result, FDA would encounter significant constitutional obstacles if it were to adopt categorical rules prohibiting truthful, non-misleading speech about medical product uses in some therapeutic areas but not others.

¹² James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA Approved Drugs*, 12 Ann. Health Law 295 (2003).

4. We heard testimony regarding the need for FDA to adjudicate “claims” and “promotion” in view of prior public health tragedies such as thalidomide and elixir sulfanilamide. What lessons should we take from those prior episodes, and how do they relate to the legislation under consideration and to the off-label communications issue more broadly?

The elixir sulfanilamide and thalidomide episodes are part of the canonical history of FDA regulation and are widely understood to have prompted Congress to enact the laws that form the basis of contemporary standards for the marketing of therapeutic products. But neither one is instructive with regard to the specific policy questions addressed in the hearing, which relate to off-label uses of approved products, rather than uses of products not approved for any purpose.

Elixir sulfanilamide was an antibiotic product introduced in the mid-1930s, before the law required any approval or proof of safety before marketing. It was formulated with diethylene glycol, which was intended to make sulfanilamide (the active ingredient) soluble and stable in a liquid form. Diethylene glycol is highly toxic, and more than 100 people died after consuming the product.

Thalidomide was introduced as a sleeping pill in Europe in the 1950s, and was used to treat morning sickness in pregnant women. It was never approved for marketing in the United States, but was distributed to U.S. doctors for investigational use before the law required FDA oversight of such use. The drug caused significant deformities in thousands of children, including 17 in the U.S.

These tragedies dramatized the need for regulatory oversight of investigational drugs, robust premarket review, and mandatory reporting of adverse events—key features of the current regulatory regime for drugs and medical devices. But neither episode involved a product that had been reviewed and approved by FDA according to the standards that exist in the law today. Moreover, these products were dangerous because of their inherent properties, and because they were made available to patients with grossly inadequate accompanying labeling and other information. As a result, they are not instructive with regard to the specific policy questions presented by the hearing, which relate to the dissemination of truthful and non-misleading information about off-label uses of lawfully marketed products.

5. We heard testimony regarding the risk of clinical decisions as a result of scientific information provided directly to prescribers without FDA intermediation. What is the proper role of FDA in regulating information as a means of encouraging prescribers to make therapy selection decisions that accord with the agency's view of patient care?

FDA determines whether medical products satisfy applicable premarket review standards under the FDCA. A constituent part of that system is the review of the labeling that accompanies a product and reflects FDA's authoritative conclusions as to the circumstances in which the risk-benefit ratio of the product can be optimized. Prescribers also obtain scientific information from scientific meetings, continuing education, medical journal articles, and other sources.

A health care practitioner may make an informed decision that a use not approved by FDA is nevertheless clinically appropriate, based on the prescriber's knowledge of the mechanism of disease, the technological principles of the product, the individual patient's medical history, and other relevant considerations.

To the extent FDA has its own views as to the proper role of an approved product in patient care, it can and does share those views with prescribers by requesting that manufacturers include clinically relevant information in product labeling and by engaging in its own communications directed to health care professionals, such as product safety alerts. But in the current statutory scheme, the agency is generally not permitted to impose its own views on prescribers, patients, payors, and other audiences as to the appropriate use of medical products.

As FDA has explained, the agency is responsible for evaluating the safety and effectiveness of drugs and medical devices and the truthfulness of their labeling. The health care practitioner "is then responsible for making the final judgment as to which, if, any, of the available" products the patient "will receive in the light of the information contained in their labeling and other adequate scientific data available to" the practitioner.¹³

¹³ 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972). *See also* 21 U.S.C. § 396 ("Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.").

6. Assuming there is agreement regarding the utility of independent FDA review of manufacturer information before it is shared with prescribers, what are the costs associated with the delay that would accompany FDA's review?

Under existing law, if a manufacturer wishes to promote a lawfully marketed product for a new use, the manufacturer is required to make a new submission to FDA and await agency authorization to market the product using the desired claim. The requirement of an additional submission to FDA is triggered only when the prospective claim promotes a "new use"—defined in the law as a new disease state or health condition. As a result, a wide variety of claims can lawfully be made by a manufacturer for an already-marketed product without any prior FDA review as long as the claims satisfy applicable statutory requirements. The claims must be truthful, non-misleading, supported by adequate data, and presented with sufficient contextual information, including information about product risks.¹⁴ Additionally, FDA has adopted several safe harbors and policies that allow manufacturers to communicate certain "off-label" information as part of scientific exchange, in response to unsolicited requests, in continuing education and analogous events, and through reprints and similar materials.

Requiring prior review would significantly restrict and delay the ability of manufacturers to communicate up-to-date information about their medical products to inform treatment decisions. As a result, the public health would be negatively affected by any across-the-board requirement of prior FDA review of manufacturer communications. For example, FDA review of supplemental applications for new indications for oncology products can take many months, and in the past such review has sometimes required years.¹⁵ In this therapeutic area, drugs are often approved based on a survival benefit of shorter duration. The human cost of the aggregated delay across all product categories is impossible to quantify.

¹⁴ See generally 21 U.S.C. §§ 321(n), 352(a), (n) & (r); 21 C.F.R. §§ 201.100(d), 202.1(e)(4) & (5)(ii).

¹⁵ FDA is subject to a performance goal of reviewing and acting on 90 percent of efficacy supplements within 6-10 months. In addition, regional variations in treatment reflect differences in physicians' access to the most up-to-date information about clinical options, and correspond to differences in outcomes based on geography. See, e.g., L. Pilote, M.D., M.P.H., et al., *Regional Variation Across The United States In the Management of Acute Myocardial Infarction*, 333 NEJM 565 (1995) (describing results of study demonstrating "marked regional variation in the management of acute myocardial infarction in the United States," including both use of medications and performance of procedures). Community-based physicians need complete and up-to-date information about treatment options and often manufacturers are the only or the best source of such information. Under the current federal regulatory system, manufacturers have some ability to provide information about emerging efficacy information across the full range of uses of medical products, and about investigational products that might be made available to patients, including through expanded access mechanisms.

The Honorable Richard Hudson

North Carolina is home to some of the finest medical research institutions in the world, with notable institutions like the University of North Carolina at Chapel Hill, Duke University, North Carolina State University and Wake Forest University, where cutting edge medical research is carried out every day. North Carolina is also home to a burgeoning life sciences industry, with over 100 small, medium, and large device and pharmaceutical manufacturers. Together, this ecosystem of innovation fosters and creates cutting edge treatments for diseases and illnesses.

Oftentimes, these innovative drugs and devices are able to be used for diseases the original FDA application did not envision. As our healthcare system moves into a value based model of patient care, where collaboration between providers and payers helps manage care to provide better long term outcomes, it is important to encourage communication about new uses for these drugs and devices to disseminate better modalities of care across our healthcare system.

1. Would you agree that it is in the public's best interest to allow the companies who produce these drugs and devices the ability, in a tailored way, to communicate with providers and payers about off-label uses? And can you elaborate on ways these companies can be helpful to both the providers and payers, whether that's through data analytics, clinical expertise, or ways to reduce costs?

Yes. The public interest is best served when decisions regarding uses of medical products are informed by truthful, accurate, and non-misleading information. Manufacturers are well-positioned provide a variety of analyses that may be helpful to providers and payers. These include, among others:

- Up-to-date case series or retrospective subgroup analysis, which may be particularly helpful in ultra-rare conditions, oncology, and similar fields where clinical practices are rapidly evolving and adequate and well-controlled data are not available.
- Healthcare economic analysis, which is particularly important given the increasing influence of value-oriented considerations on health care delivery.
- Analysis of data obtained in the real world, including data from electronic health records, claims and billing activities, product and disease registries, and mobile devices, which offers the potential for information that can be based on larger sample sizes with a broader range of patients, and can be more up-to-date, than data from randomized controlled clinical trials.

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS
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August 17, 2017

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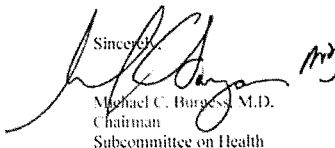
Dear Ms. Charo:

Thank you for appearing before the Committee on Energy and Commerce on July 12, 2017, to testify at the hearing entitled "Examining Bipartisan Legislation to Improve the Medicare Program."

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.

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on August 31, 2017. Your responses should be mailed to Zack Dareshori, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to zack.dareshori@mail.house.gov.

Thank you again for your time and effort preparing and delivering testimony before the Committee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

Attachment- Additional Questions for the Record**The Honorable Michael C. Burgess**

1. We heard testimony as to the need for FDA to act as a "learned intermediary" between manufacturers and prescribers with respect to scientific information disseminated under the proposed legislation. Would it represent a significant shift in federal medical product regulation if the law were to require all manufacturer communications to be reviewed by FDA in advance? What is the scope of FDA's authority under current law to substitute its judgment for that of a prescriber when it comes to drug and medical device use?

RESPONSE: It would be unusual for the government to take on the task of reviewing all communications in advance, as this would certainly face powerful challenges under the First Amendment. Prior restraint of speech is given much stricter scrutiny than post-speech review and request for correction of false or misleading statements. As to substituting the judgement of a prescriber, FDA has fairly limited authority. Providers are free to prescribe off-label, based on their own judgement, and subject to quality controls in the form of state licensing and disciplinary boards, or medical malpractice suits, if their judgement proves to be at odds with the standard of care.

2. We heard testimony regarding the inability of any manufacturer to provide complete information about a new use. It was also suggested that FDA is the only source of complete information about the full range of medical product uses. What information does FDA receive from manufacturers, adverse event reporting, and other sources, and how does that information compare to the data and analysis to which the manufacturer has access?

RESPONSE: Because submissions to FDA are confidential, it is possible at times that FDA will be aware of multiple sponsors testing similar formulations in various pre-clinical and clinical trials. As a result, FDA may know from Sponsor X that a particular side effect is possible, or that a particular interaction with another drug is problematic, but Sponsor Y – who is testing a similar drug – will not have this information.

3. It has been suggested that off-label information might be more useful in some areas of practice than in others. How should the subcommittee evaluate that issue, and is there a principled basis in the law for making a distinction in the regulation of information dissemination according to the nature of the disease area (e.g., rare diseases, oncology) or patient population (e.g., pediatrics)?

RESPONSE: In an ideal world this might be possible, but in reality it would not be easy to make clean categories that separate the tightly regulated from the loosely regulated. That said, one might take advantage of some existing distinctions, e.g. for those products that are being reviewed as 'orphan drugs' due to the rarity of the condition.

4. We heard testimony regarding the need for FDA to adjudicate "claims" and "promotion" in view of prior public health tragedies such as thalidomide and elixir sulfanilamide. What lessons should we take from those prior episodes, and how do they relate to the legislation under consideration and to the off-label communications issue more broadly?

RESPONSE: The risk with off-label promotion is that a drug tested for one purpose/dose/population will now be disseminated quickly for a new use/dosage/target population. Expanding the range of uses and users is a way to increase profits during the crucial post-approval years when there is some market exclusivity (i.e. before generics drive prices and profits down.) But the absence of a round of trials specific to these new uses/doses/target populations means that any indication of a problem, whether toxicity or lack of effectiveness, will likely not be visible to providers or even to the sponsor-company itself. The business model drives toward rapid expansion of sales at the very same time that the lack of trials for a supplemental labeling will hinder the ability to confirm the safety and efficacy of the expanded applications.

5. We heard testimony regarding the risk of clinical decisions as a result of scientific information provided directly to prescribers without FDA intermediation. What is the proper role of FDA in regulating information as a means of encouraging prescribers to make therapy selection decisions that accord with the agency's view of patient care?

RESPONSE: FDA regulates the quality of the products and the information on the labels. It does not regulate the practice of medicine. The FDA has a proper role as a unbiased source of information about what is known about the risks and benefits of the product for various diseases and populations. This should inform provider judgement but it does not control it.

6. Assuming there is agreement regarding the utility of independent FDA review of manufacturer information before it is shared with prescribers, what are the costs associated with the delay that would accompany FDA's review?

RESPONSE: It is hard to answer this without specifics – length of delay, urgency of patient needs, number of patients, and degree of sub-optimal prescribing in the absence of a neutral eye confirming that the information given to providers is complete and neither false nor misleading.

The Honorable Frank Pallone, Jr.**Pre-Approval Communication and Intent to File**

As you know, the discussion draft released Representative Guthrie would allow drug and device manufacturers to communicate certain information to payors and other entities about an unapproved use of a drug or device, so long as the manufacturer "intends" to submit a supplemental application to FDA in the future with evidence that the use of the product is safe and effective. However, unfortunately, what constitutes intent is left undefined in this draft. I have concerns that this preapproval communication may expand unproven uses and may create a pathway for manufacturers to increase access to therapies that may not be effective.

Q1: What is your view of this language? Do you understand how this provision could be implemented? Is the language sufficient to bind a drug or device manufacturer to actually go through the application process?

Q2: You noted in your testimony that this provision could result in increased patient use of unproven or unsafe therapies. Can you explain how?

Q3: Without clearly defining what constitutes intent, could this create a loophole for manufacturers?

Q4: Is there an enforcement mechanism available to FDA either from the discussion draft, or through current law, in the case where a manufacturer ultimately decides not to seek approval for this indication after it has shared information with the payer?

RESPONSE: *Please allow me to respond to all four questions in an integrated fashion. I share the concern about a provision that hinges on the 'intent' of the sponsor. Certainly a sponsor might have a genuine intent to come at a later date to the FDA but nonetheless find that circumstances have changed and that the planned action is no longer in the sponsor's interest. Indeed, the experience of patients who are the subjects of the now-promoted off label use may demonstrate the risks or lack of benefits that would lead the sponsor to change its plans. In a sense, this is a form of unregulated, uncontrolled research with the patients who are the subject of the off-label use, and without any of the usual protections. The patients would not realize they were experimental subjects, would often be paying for the product (whereas in a clinical trial they might well get it free), and would not be assured that there is an oversight body monitoring the patient experiences in a rigorous way with a capacity to cease use of the product if there are indications its risks exceed its benefits.*

Promotional Speech

During the hearing there was considerable discussion over the distinctions between promotional and non-promotional communication, and whether or not the proposed discussion draft offered by Representative Griffith would protect against promotional communication by a manufacturer of scientific information.

- Q1:** Will you discuss further the distinctions between non-promotional and promotional communication by a medical product manufacturer, and how those two have been defined in case law?
- Q2:** What is your view of the discussion draft released by Rep. Griffith? Does this draft adequately protect against promotional communication by a manufacturer? If so, what enforcement tools would be available to FDA to ensure that manufacturer communications are truthful, non-misleading, and non-biased, and limited to the sharing of appropriate non-promotional scientific information?

RESPONSE: The distinction between promotional and non-promotional speech can at times be subtle, and often relies upon context. For example, distributing a peer-reviewed article from a respected scientific journal about possible off-label uses would not in itself be promotional, but it would be promotional if it were accompanied by clearly promotional literature aimed at encouraging purchase of the product in order to prescribe it for the off-label use, or if the article is presented as if it were definitive when in fact there are many other articles from equally respectable sources that come to contrary conclusions. This is why FDA has published guidances that lay out best practices which, if followed, act as a 'safe harbor' for sponsors who distribute such information.

GREG WALDEN, OREGON
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August 17, 2017

Dr. George Van Hare
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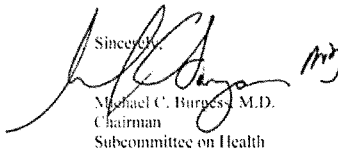
Dear Dr. Van Hare:

Thank you for appearing before the Committee on Energy and Commerce on July 12, 2017, to testify at the hearing entitled "Examining Bipartisan Legislation to Improve the Medicare Program."

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.

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Thank you again for your time and effort preparing and delivering testimony before the Committee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

ANSWERS BY DR. VAN HARE, HEART RHYTHM SOCIETY, TO QUESTIONS FOR THE RECORD
RELATED TO:

“EXAMINING BIPARTISAN LEGISLATION TO IMPROVE THE MEDICARE PROGRAM”
ENERGY & COMMERCE COMMITTEE, JULY 12, 2017

The Honorable Michael C. Burgess

1. **We heard testimony as to the need for FDA to act as a “learned intermediary” between manufacturers and prescribers with respect to scientific information disseminated under the proposed legislation. Would it represent a significant shift in federal medical product regulation if the law were to require all manufacturer communications to be reviewed by FDA in advance? What is the scope of FDA’s authority under current law to substitute its judgment for that of a prescriber when it comes to drug and medical device use?**

FDA already reviews pharmaceutical advertisements in advance, in part due to the fact that these are disseminated to the public at large. The risk for misinterpretation is greater in the case of information disseminated directly to the public than in the case of information disseminated to healthcare professionals, who are trained to analyze clinical and scientific information. By law, communications with healthcare professionals must be truthful and non-misleading, but they receive no pre-distribution review from the agency. Rather, the prescriber is the “learned intermediary” between the manufacturer and the patient. It is unlikely that adding FDA review as an additional step will accomplish much other than slowing down the distribution of clinical data and diverting precious agency resources from its main mission with regard to pharmaceuticals and devices, which is to ensure the safety and efficacy of these products.

2. **We heard testimony regarding the inability of any manufacturer to provide complete information about a new use. It was also suggested that FDA is the only source of complete information about the full range of medical product uses. What information does FDA receive from manufacturers, adverse event reporting, and other sources, and how does that information compare to the data and analysis to which the manufacturer has access?**

FDA may receive a broader range of information than the manufacturer can provide, as most of the manufacturer’s data will be related only to its specific product. For example, FDA may sooner flag a safety issue with a class of drugs, given that the agency would receive adverse event reports related to the entire class, rather than just a single member of the class. Conversely, FDA would not be in receipt of “real-world” evidence, such as observational studies, pharmacoeconomic studies, or information on subpopulations that is gathered by the manufacturer in post-market settings. Both kinds of data are useful to clinicians and we are eager to receive them, as long as the data are truthful, presented in context, and scientifically valid.

3. It has been suggested that off-label information might be more useful in some areas of practice than in others. How should the subcommittee evaluate that issue, and is there a principled basis in the law for making a distinction in the regulation of information dissemination according to the nature of the disease area (e.g., rare diseases, oncology) or patient population (e.g., pediatrics)?

As someone who specializes in pediatric cardiology, I am particularly appreciative of this question as it is an indisputable fact that off-label information is critical for certain populations and diseases. Especially with regard to these populations, it is important to note that off-label uses are often not experimental uses. In fact, some are so common they have become the standard of care. Many off-label uses are well-documented in the peer-reviewed literature, are discussed widely among physicians, and are cited as standard uses in medical textbooks. For me and other pediatric subspecialists – as well as clinicians who treat rare diseases – off-label use of drugs or devices is not a choice. It is a necessity. For example, very few of the currently marketed medications for arrhythmias are formally approved for use in children. Thus, using treatments off-label is often our main method of treatment.

Under the current regulatory paradigm, we do not get the benefit from any data that is not derived from a randomized, controlled clinical trial. Unfortunately, that means we do not receive any data related to pediatric populations, as these are still not well-represented in clinical trials, despite regulatory incentives for manufacturers to include them. While there are an additional six months of exclusivity granted to manufacturers who generate data related to pediatric populations under the Pediatric Research Equity Act (PREA), this has not been sufficient to produce the amount of shareable data we might like, particularly for older drugs. As such, our clinical decisions often rest on anecdotal evidence and informal information-sharing among physicians. This is not an ideal environment in which to make treatment decisions, and it does not inspire confidence in the parents of these children with regard to the available drugs and devices.

It is difficult to articulate a principled basis in law by which to make a distinction in the information that may be disseminated. A better approach would be to let manufacturers share with clinicians data that is truthful, presented in context, and scientifically valid. Barring that, at a minimum, clinicians treating rare diseases or diseases in pediatric populations should have access to all data within those parameters.

4. We heard testimony regarding the need for FDA to adjudicate “claims” and “promotion” in view of prior public health tragedies such as thalidomide and elixir sulfanilamide. What lessons should we take from those prior episodes, and how do they relate to the legislation under consideration and to the off-label communications issue more broadly?

In the late 1930s, the fatalities caused by “Elixir Sulfanilamide” resulted in creation of the Food, Drug, and Cosmetic Act. Similarly, the serious consequences arising from use of thalidomide during pregnancy was the result of marketing in the 1950s and 1960s – long

before the FDA's current, rigorous safety standards around clinical trials and off-label promotion were in place. Indeed, the thalidomide tragedy was a catalyst for the creation of many of these standards. These examples illustrate the dangers of allowing promotional claims to the public that are not scientifically sound and not truthful.

However, there is a difference between advertising an unapproved use to the public and sharing scientifically valid data with clinicians, and this difference can be reflected in the regulatory approach to each type of activity. There is a vast space between our current regulatory approach and the "Wild West" environment that allowed any sales (let alone promotion) of a poisonous product like "Elixir Sulfanilamide" and unfettered promotion of a product harmful to fetal development like thalidomide.

Considering our current standards related to clinical trial and drug approval, the key question in the context of off-label information is: what is promotion? The answer to that may differ based on the audience. Physicians are trained to analyze data; we know how to evaluate the validity of studies. If regulatory restrictions ensure that the data is truthful and presented in context, physicians can analyze such data effectively. Unfortunately, the current regulatory approach limits the ability of a manufacturer to share any data that is not referenced in the package insert. That means a lot of valuable information may never be conveyed to clinicians and other medical decision-makers.

5. **We heard testimony regarding the risk of clinical decisions as a result of scientific information provided directly to prescribers without FDA intermediation. What is the proper role of FDA in regulating information as a means of encouraging prescribers to make therapy selection decisions that accord with the agency's view of patient care?**

As noted above, FDA's role should be to ensure that any data shared with clinicians is truthful, presented in context, and scientifically valid. For the reasons noted above, a pre-dissemination review of information intended for physicians would not be helpful and would slow down the distribution of information. A better approach would be for FDA to define, via notice-and-comment rulemaking which would allow for input from stakeholders, what constitutes truthful, presented in context, and scientifically valid, and then utilize its various enforcement tools for manufacturers who distribute information that fails to meet those standards.

6. **Assuming there is agreement regarding the utility of independent FDA review of manufacturer information before it is shared with prescribers, what are the costs associated with the delay that would accompany FDA's review?**

While I cannot make specific budgetary predictions from the agency's perspective, as noted above, I would be concerned that a new, independent review function would divert resources from the agency's main functions. From the provider perspective, this would slow down the dissemination of clinical data – even the data we can readily receive under

current law. Outdated clinical information is not helpful for prescribers and, in turn, comes with a cost to patients.

The Honorable Richard Hudson

Would you agree that it is in the public's best interest to allow the companies who produce these drugs and devices the ability, in a tailored way, to communicate with providers and payers about off-label uses? And can you elaborate on ways these companies can be helpful to both the providers and payers, whether that's through data analytics, clinical expertise, or ways to reduce costs?

I agree that manufacturers sharing data with clinicians, particularly those treating patients with rare diseases and children, is in the public's best interest, provided that the data is truthful, presented in context, and scientifically valid. For example, manufacturers may have real-world, post-market evidence indicating that their product is not as effective in a particular subpopulation. That would be valuable for clinicians to know, as it would prevent us from using the product in a population that may not benefit from it sufficiently to offset any safety risks. While any physician is nervous about providing more information to payers in a quest to reduce costs, a payer may wish to have such information as well, given that it could prevent spending resources on a product that will ultimately not help the patient.

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August 17, 2017

Dr. Aaron S. Kesselheim
Associate Professor of Medicine
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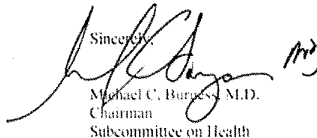
Dear Dr. Kesselheim:

Thank you for appearing before the Committee on Energy and Commerce on July 12, 2017, to testify at the hearing entitled "Examining Bipartisan Legislation to Improve the Medicare Program."

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Thank you again for your time and effort preparing and delivering testimony before the Committee.

Sincerely,

Michael C. Burgess, M.D.
Chairman
Subcommittee on Health

cc: The Honorable Gene Green, Ranking Member, Subcommittee on Health

Attachment

[Mr. Kesselheim did not answer submitted questions for the record by the time of printing.]

Attachment — Additional Questions for the RecordThe Honorable Michael C. Burgess

1. We heard testimony as to the need for FDA to act as a “learned intermediary” between manufacturers and prescribers with respect to scientific information disseminated under the proposed legislation. Would it represent a significant shift in federal medical product regulation if the law were to require all manufacturer communications to be reviewed by FDA in advance? What is the scope of FDA’s authority under current law to substitute its judgment for that of a prescriber when it comes to drug and medical device use?
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4. We heard testimony regarding the need for FDA to adjudicate “claims” and “promotion” in view of prior public health tragedies such as thalidomide and elixir sulfanilamide. What lessons should we take from those prior episodes, and how do they relate to the legislation under consideration and to the off-label communications issue more broadly?
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6. Assuming there is agreement regarding the utility of independent FDA review of manufacturer information before it is shared with prescribers, what are the costs associated with the delay that would accompany FDA’s review?

The Honorable Frank Pallone, Jr.**Dangers of Expanding Scientific Exchange**

In your testimony you provided a number of examples of past instances where manufacturers have settled with the federal government over inappropriate off-label promotion. However, you noted importantly that many of these examples were not manufacturers spreading falsehoods, but rather providing anecdotal benefits from uncontrolled cases, flawed observational studies, or selectively presenting only favorable studies.

The proposed discussion draft offered by Representative Griffith would create a “scientific exchange safe harbor” which would allow a manufacturer to engage in communication as long as that communication is not advertising or promotional in nature, is supported by competent and reliable scientific evidence, provides contextual information about the data presented, and discloses that such information is not in the labeling and that the unapproved use has not been found to be safe and effective.

- Q1:** Does the criteria outlined in Rep. Griffith’s discussion draft guard against some of the bad behavior you note in your testimony, such as the anecdotal evidence from uncontrolled case series, unbalanced study data, or favorable presentation of literature? If not, what further safeguards would be necessary to protect against such behaviors?
- Q2:** Both of the proposed discussion drafts that were the focus of the hearing include disclaimers that intend to make clear that the drug or device has not been proven to be safe and effective or to clarify the differences between the information provided and what is included in the labeling. Given your research in this area, do you believe the inclusion of such disclaimers in the discussion drafts will help to clarify for patients and providers that the information provided is not associated with an approved use or an approved product?

Off Label Communication with Physicians

We have heard from some health care providers that under current Food and Drug Administration (FDA) guidance and regulations physicians are unable to receive timely access to clinical information that could be useful in making patient care decisions. Some have also argued that health care providers are trained and able to analyze data to know when a study is misleading, or when the data is presented with bias or out of context, making them a skeptical audience for manufacturer communication.

In your testimony, you noted the value of having FDA provide an independent assessment of whether a drug or high-risk medical device is safe and effective for its intended use, and in fact suggest FDA is an important intermediary for prescribing physicians as not all physicians have the time and expertise to scrutinize claims from manufacturers.

- Q1:** As a physician yourself, do you believe further legislative safe harbors are needed in order to ensure physicians have access to timely and sufficient scientific information? And if so, how do we ensure that such safe harbors don’t result in the collection and dissemination of less rigorous data to physicians?
- Q2:** Can you discuss further what impact, if any, increased off label communication from manufacturers may have on physician behavior?

Off-Label Promotion and Prescribing Practices

In response to a question from Congresswoman Schakowsky, you noted that history has shown that off-label promotion drives physician practices “in ways that favor the drug being promoted, not in ways that favor the overall state of the evidence and the overall state of practice.”

- Q1:** Is there evidence demonstrating that there is a direct association between promotional statements and prescribing practices? If so, please discuss this association further.
- Q2:** In reviewing the proposed discussion drafts released by Reps. Griffith and Guthrie, what further changes are necessary to ensure that the communications contemplated under the “scientific exchange safe harbor” and the “preapproval information exchange” are not promotional?

ClinicalTrials.gov

At the hearing there was a discussion about the utility and effectiveness of ClinicalTrials.gov and the availability of clinical trials information for physicians. Ms. House commented on the difficulty of patients in finding information about relevant treatments. Ms. Khachatourian commented that the frequent delay of publication of clinical trial information also makes it difficult for payors to make coverage decisions.

- Q1:** How can we better utilize, or improve, ClinicalTrials.gov to ensure that patients and physicians have access to timely and useful scientific or medical information about medical products? Could such improvements help to alleviate the need for expanding manufacturer communication about unapproved products or uses of products?

GREG WALDEN, OREGON
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS
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August 17, 2017

Ms. Linda House
President
Cancer Support Community
734 15th Street, N.W.
Suite 300
Washington, DC 20005

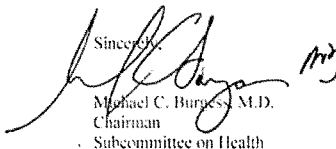
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The Honorable Michael C. Burgess

1. We heard testimony as to the need for FDA to act as a “learned intermediary” between manufacturers and prescribers with respect to scientific information disseminated under the proposed legislation. Would it represent a significant shift in federal medical product regulation if the law were to require all manufacturer communications to be reviewed by FDA in advance? What is the scope of FDA’s authority under current law to substitute its judgment for that of a prescriber when it comes to drug and medical device use?

I cannot speak specifically to the current regulation. I will say that CSC does support responsible communication by the manufacturer and also FDA regulation of promotional communication. However, adding a requirement that the FDA review all communication would create a significant burden on the system that I believe would cause delays in the exchange of timely and meaningful information. The question, as written, does not differentiate between promotional communication (e.g., print and TV ads) and scientific exchange (e.g., sharing the results of a new trial). Imagine being a provider seeing a patient who has a rare cancer in your office. You are aware that an investigator worked with a manufacturer on an investigator-initiated trial (IIT) for that rare cancer. In the model you propose, in order for the provider to gain access to the results of that IIT, the provider would have to wait until the manufacturer cleared their response with the FDA before providing an update on the trial. Additionally, in the current system, the FDA may not have results from the many IITs performed through the vast investigator network. If the policy outlined above were to change, so too would the requirements around reporting, database updating, and rapid labeling changes, to name a few. Further, CSC believes that the “learned intermediary” should be reframed as a “learned informer” to ensure that patients have comprehensive information about their illness and the options available to them. This “learned informer” role sits best as a part of the compact that exists between the patient and their provider – who knows the patient’s unique scenario better than anyone.

2. We heard testimony regarding the inability of any manufacturer to provide complete information about a new use. It was also suggested that FDA is the only source of complete information about the full range of medical product uses. What information does FDA receive from manufacturers, adverse event reporting, and other sources, and how does that information compare to that data and analysis to which the manufacture has access?

This question should be directed to the FDA. I will suggest that neither the FDA nor the manufacturer has complete information about the full range of medical product uses once the product is commercially available. To the extent of my knowledge, the FDA has access to the clinical trial datasets, the label submission datasets, and adverse event reporting. I do not believe that the FDA has full access to information learned from the IIT trials mentioned above, as one example. These trials often study novel uses, doses, and administration and offer meaningful contributions to the body of evidence generally, but especially for rare diseases.

3. It has been suggested that off-label information might be more useful in some areas of practice than in others. How should the subcommittee evaluate that issue, and is there a principled basis in the law for making a distinction in the regulation of information dissemination according to the nature of the disease area (e.g., rare diseases, oncology) or patient population (e.g., pediatrics)?

To the best of my knowledge, there is no distinction in the regulation. The use of off-label information is more effective and likely more prevalent in rare diseases and other scenarios where there is high unmet need. The complexity of the topic would require a cross-functional approach led by individuals with deep expertise. If the subcommittee feels it is within their frame to evaluate this, it should convene a working group of individuals from the FDA, manufacturers, providers, patient groups, and patients to discuss and recommend new approaches that work to improve patient outcomes.

4. We heard testimony regarding the need for FDA to adjudicate “claims” and “promotion” in view of prior public health tragedies such as thalidomide and elixir sulfanilamide. What lessons should we take from those prior episodes, and how do they relate to the legislation under consideration and to the off-label communications issue more broadly?

It should always remain the role of the FDA to ensure patient safety. This role has typically entailed ensuring that solutions are safe and effective for use. Post-commercialization, this focus on safety has primarily centered on toxicity (e.g., side effects and other disease related events). As the environment continues to evolve and personalized medicine continues to turn macro-level diseases (e.g., lung cancer) into highly specialized diseases (e.g., ALK+ lung cancer), the system and focus need to follow this evolution to embrace findings from trials that support evidence-based, real-world data on these highly-specialized populations. Regulatory statute and review systems should also evolve to ensure that patients and providers have access to sufficient information to make fully informed decisions about care and both the safety and efficacy components of the risk/benefit trade-off.

5. We heard testimony regarding the risk of clinical decisions as a result of scientific information provided directly to prescribers without FDA intermediation. What is the proper role of FDA in regulating information as a means of encouraging prescribers to make therapy selection decisions that accord with the agency’s view of patient care?

The FDA should ensure that information communicated to providers and patient is evidence-based, peer reviewed, and scientifically sound. In the current environment, FDA regulation focuses on communicating use directly from more narrow sources including the controlled clinical trials performed for product labeling, the actual label itself, and toxicity reported through post-marketing surveillance. As has been noted in multiple reports and forums, the FDA labels are oftentimes out of date and may not contain information on rare disease populations or the highly specialized diseases referenced above, yet there may be perfectly safe and meaningful data available through other resources that may never become available to patients and clinicians because of the currently regulatory statute and FDA limitations.

6. Assuming there is agreement regarding the utility of independent FDA review of manufacturer information before it is shared with prescribers, what are the costs associated with the delay that would accompany FDA's review?

It is difficult to answer this with any level of specificity, but the costs associated with the delay that would accompany the FDA review would be directly related to the costs associated with the delay in starting treatment for patients. I think about the patient with an aggressive cancer where hours matter waiting to hear about a treatment option, or a patient with sepsis where seconds and minutes matter waiting to hear about a treatment option. Imagine if there is scientifically-validated information to help these patients, available in peer-reviewed journals, but these patients have to wait for it to be approved for dissemination by the FDA. Instead, imagine a system that would create enforceable guardrails to allow immediate dissemination of information to providers and patients as soon as the information reaches an acceptable threshold of evidence.

The Honorable Tony Cardenas

Ms. House, according to the American Cancer Society, a recent survey has shown that a majority of practicing oncologists prescribe drugs off-label to treat cancer. In fact, off-label prescription of drugs has become so common for the treatment of cancer that the National Cancer Institute (NCI) has stated, "Frequently, the standard of care for a particular type or stage of cancer involve[s] the off-label use of one or more drugs."

1. Can you help us to understand how and why utilizing drugs off-label, including not just for different indications but also for novel or unique dosing or routes of administration, can be important to the practice of oncology?

As the environment continues to evolve and personalized medicine continues to turn macro-level diseases (e.g., lung cancer) into highly specialized diseases (e.g., ALK+ lung cancer), the system and focus need to follow this evolution to embrace findings from trials that support evidence-based, real-world data on these highly-specialized populations. One example regarding unique dosing is the use of Gemcitabine for the treatment of pancreatic cancer. The Gemcitabine label instructs that the treatment should be administered by 30-minute infusion. There was an early and ongoing hypothesis that administering Gemcitabine over a longer period of time (coined fixed-duration infusion) would essentially saturate cells with more drug and thus produce higher cell death and prolong patient survival. There was also a concern that fixed-duration infusion could increase toxicity. In the years since Gemcitabine received its label, studies have been done on hundreds of patients and published in peer-reviewed journals (e.g., Journal of Clinical Oncology), yet this information might not be available for patients and clinicians to access and the Gemcitabine label will likely not be updated to reflect these findings.

2. What types of data would be most useful during scientific exchange and are there existing best practices for distinguishing these data from those in approved labeling?

As a baseline, all data should be peer-reviewed and/or fully vetted by third party independent reviewers. The scientific rigor required for acceptance to journals like the Journal of Clinical Oncology, the New England Journal of Medicine, or the Journal of the American Medical Association should pass the standard of communication to providers and patients. Such communication and data should be clearly indicated as outside the scope of the FDA label and supplemental, for use in treatment decision-making conversations between providers and patients.

3. What safeguards need to be developed in order to prevent bad actors from manipulating a system of scientific exchange optimized for responsible manufacturers of medical products?

There should be clear guidance in place – and enforced – to set expectations of the types of data which can be shared, how it can be shared, and consequences for violating the guidance. Managing to the bad actors at the expense of access to information for comprehensive treatment decision-making for the masses seems detrimental to overall patient care.

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August 17, 2017

Ms. Kat Khachatourian
Vice President
Qualchoice Health Plan Services
33820 Weyerhaeuser Way South
Heron Building, 2nd Floor
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The Honorable Frank Pallone, Jr.**Pre-Approval Communication Safeguards**

The proposed discussion draft offered by Representative Guthrie relating to pre-approval communication proposes to allow medical product manufacturers to share health care economic information and scientific information about new indications and new products. I am concerned because the discussion draft would include a broad expansion of what can be communicated,

while also carving out any of FDA's enforcement authorities, leaving the agency hamstrung in its ability to ensure such communication is truthful and not misleading.

Q1: You note in your testimony that there is a need for a minimum set of standards that information shared in a pre-approval context must meet. What principles should such standards encompass? For example, what should the minimum levels of evidence be for such communication? Further, what standards should be put in place to protect against the sharing of non-truthful and misleading information?