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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, D.C.

The subcommittee met, pursuant to call, at 10:15 a.m., in Room 2322 Rayburn House Office Building, Hon. Michael 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, Cardenas, 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, External Affairs; Jeff Carroll, Minority Staff Director; Samantha Satchell, Minority Policy Analyst; Andrew Souvall, Minority Director of Communications, Outreach and Member Services; 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.

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 non-misleading information about products approved by the Food and Drug Administration.

I practiced medicine for several decades. I know firsthand how challenging it is it 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 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 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 non-misleading 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 approached 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.

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 pre-approval 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 into the record by a number of organizations including the Academy of Managed Care Pharmacy, Humana, Sanofi, and Mayo Clinic.

Mr. Burgess. Without objection, so ordered.

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 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 non-misleading 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.

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.

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 for 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 non-promotional manner by manufacturers.

The FDA has attempted to address this issue, but it has been in a piecemeal fashion or the last 2 decades with various non-binding 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 non-misleading 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.

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 non-misleading 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 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 healthcare economic information with payers to help them better understand the economic benefits of an approved

treatment.

These are common-sense 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 pre-approval 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 non-peer 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.

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 records.

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.

STATEMENT OF COLEEN KLASMEIER, PARTNER; SIDLEY AUSTIN LLP; ALTA CHARO, WARREN P. KNOWLES PROFESSOR OF LAW, UNIVERSITY OF WISCONSIN; GEORGE VAN HARE, CO-DIRECTOR, 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 HOPSITAL; LINDA HOUSE, PRESIDENT OF THE CANCER SUPPORT COMMUNITY; AND KATHERINE WOLF KHACHATOURIAN, VICE PRESIDENT, DELEGATION OVERSIGHT, PHARMACY SERVICES OF QUALCHOICEHEALTH PLAN SERVICES

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, D.C. 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, 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. They therefore lack the force of law. Moreover, two of the four safe harbors have been the subject of on-going 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 challenge 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:]

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Mr. Burgess. I thank the gentlelady for her testimony.

Ms. Charo, you are recognized for 5 minutes, please.

STATEMENT OF 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:]

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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:]

**********INSERT 3**********

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 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 pre-clinical 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:]

**********INSERT 4*********

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 collet, 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, non-promotional communication.

Pre-approval 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:]

**********INSERT 5**********

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 patience 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 approval. 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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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 on line 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 on line 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. Okay. 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, okay. 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 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 goverment loses. So strict scrutiny is a bit of a legal

fiction that we indulgence. 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 non-evidenced based -- potentially non-evidenced 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 therapies 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 two thirds 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 two, 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.

Mr. Griffith. It goes 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 manufacturers 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 non-promotional 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. Okay. 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 gentleman 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-N. 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. Not 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 non-promotional 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 non-promotional 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 back drop 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 speech that is about -- 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 D.C. 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 memoranda 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 short cut. 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, etcetera?

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 anti-malarial 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 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 D.C. 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

say 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 non-promotional 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 countless 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 to the chairman 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.

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

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