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Policy Options for Off-Label Communication: Supporting Better Information, Better Evidence, and Better Care

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Introduction

The regulation of methods for communicating about off-label use of medical products approved by the U.S. Food and Drug Administration (FDA) has long been a challenging area of policymaking**.** On the one hand, new steps to facilitate the development and dissemination of accurate information about off-label uses of medical products could lead to a better understanding of the relevant evidence by providers, patients, payers, and others who make or influence treatment decisions. This could lead to better decisions for many patients: estimates suggest that around 40% of overall prescribing decisions are off-label, as are most decisions in some critical areas like cancer care.[1] By some accounts, these rates appear to be rising. On the other hand, such policy changes could lead to more instances of evidence being taken out of context or used inappropriately without being submitted to FDA for rigorous independent regulatory review, leading to harm or added costs for patients and potentially undermining the incentives for developing evidence that is good enough to be placed in approved drug labeling.[2]

The policy debate around off-label communication is further complicated because sharing off-label information can be understood in two different conceptual and legal frameworks. Off-label communications that can be linked to marketing through efficacy claims are subject to FDA's regulatory authority under labeling and advertising provisions in current law. These off-label promotional activities are an area of public health concern because of their potential to undermine the objectives of the legal framework of drug regulation. More general communications around emerging studies or data, however, are typically described as outside the scope of the agency's regulatory authority. Such communication can play an important role in advancing health care knowledge.

Yet there is a fine line between promotion and pure information dissemination, and disagreements about how to characterize certain activities have generated litigation and conflict. Indeed, the courts have rejected on First Amendment grounds several attempts to enforce certain restrictions on off-label communication. The resulting uncertainty has led to an unsatisfactory and unsustainable patchwork of regulations, guidance documents, and agency practices related to off-label communication, product labeling, and scientific exchange of information. The range of agencies that can enforce the prohibition on off-label promotion—not only the FDA, but also the Federal Trade Commission (FTC), Department of Health and Human Services (HHS) Office of the Inspector General (OIG), the Department of Justice (DOJ), and state attorneys general under the False Claims Act and state consumer protection statutes—complicates the picture still further. The absence of settled policy and clear guidance may create additional disincentives for manufacturers to invest in developing better evidence.

Responding to these challenges, bipartisan legislative efforts as well as multi-stakeholder collaborations such as the Medical Information Working Group (MIWG) have sought to develop a path forward to achieve more sustainable, effective, and clear policies on off-label communication. The FDA has also indicated interest and taken steps intended to achieve the same goals of supporting more effective communication about existing evidence and the development of better evidence for patients. In this white paper, we have collaborated with a working group of subject matter experts to provide an overview of the key issues at play in defining and regulating off-label communication, attempts to improve such communication to-date, and policy options for making real progress.

The Need for Off-Label Use and Continued Evidence Development

The Spectrum of Off-Label Use

Prescribing a medial product "on-label" involves an instruction written by a medical practitioner that authorizes a patient to be provided a therapy that has been approved by the FDA as safe and effective for the uses and conditions indicated in the FDA-approved product labeling. "Off-label" prescription, then, involves the use of a medical product in a manner that

has not been reviewed and approved by the FDA as safe and effective and that does not appear in the FDA-approved labeling. "Off-label" does not necessarily imply that risks outweigh benefits, or even that a use is unlikely to be beneficial. Rather, it is a reflection of the legal authority that leaves treatment decisions to health professionals – the FDA does not have regulatory authority over prescribers' off-label use decisions as part of the practice of medicine – and of the evidence available to use in those decisions.

Off-label prescribing and use can take many forms, such as use of an approved drug for an unapproved clinical indication, use at an unapproved dosage, use as first-line therapy in narrowly defined clinical populations where available treatment options are lacking (e.g., pediatrics or geriatrics), or use in areas where treatment options are limited or have been exhausted (e.g., oncology or rare diseases). Off-label prescribing often involves areas of high unmet medical need, and is increasingly utilized with the goal of individualizing patient treatment based on a broad array of sources of evidence.

Evidence Needs and Clinical Practice

While off-label use is an integral part of medical practice, the sources of potentially relevant data and information that may be useful for medical decisions are increasingly diverse. Drug compendia, medical and clinical practice guidelines, continuing education opportunities, primary literature, decision support tools, and other existing and emerging sources of evidence on medical products may help, but the wide array of research and resources that interpret this evidence can be unwieldy for providers or even health care systems to make fully informed decisions. Published scientific literature alone adds over 800,000 new citations each year to MEDLINE, which only represents an estimated 43% of all new annual citations in the US.[3] Keeping up with the emerging evidence within this body of literature can be daunting, and is especially difficult for primary care physicians who see patients with wide-ranging conditions, providers in rural areas or without access to large academic medical centers, and staff with very limited time between appointments to review new clinical findings.

Changes in the health care system over the past several years have further enhanced the need for communication about evidence. With a growing emphasis on value and on payment and coverage mechanisms that are linked to evidence and results, payers and providers need information to meet performance benchmarks, assess value, improve the quality of care, and establish formularies for coverage and reimbursement that are based on the best evidence available. Such decisions are not generally made based only on the information contained in the product labeling, and stakeholders regularly look outside the scope of such information to assess the utility and value of medical products. Physicians in specialty areas, for example, rely increasingly on peer-reviewed clinical practice guidelines proposed by specialty societies based on clinical meta-analysis and practice experience. The increasing use of electronic data in the health care system in turn creates the potential for further development and use of "real world" evidence that often does not reach the level of certainty needed for inclusion on the product labeling. Finally, the evolution of patients as equal partners in their own treatment decisions creates further needs related to off-label communication involving non-professional audiences.

As a result of these trends, a tremendous amount of information not incorporated into product labeling is generated within the health care ecosystem, providing even more data and analysis that could be the basis for better evidence. Any path forward will need to acknowledge the critical role that this evidence will play in an era of increasingly personalized treatments, encourage greater development of such evidence to improve the value of care, and promote sensible, scientifically-sound communication practices that ensure patients and providers have the information they need to make fully-informed choices.

The Current Off-Label Communication Landscape

FDA Regulation and Guidance

Over the last 35 years, FDA has issued a number of policy documents addressing off-label communication. In 1982, FDA published a one-page guidance to manufacturers explaining that materials provided to physicians in response to unsolicited requests would not be regarded as labeling and therefore could lawfully include information about off-label uses.[4] The unsolicited requests policy has continued in effect, with modifications reflected in later iterations published in 1994[5] and 2011.[6] Another important "safe harbor" policy permitting manufacturers to provide off-label information arises under the "scientific exchange" regulation promulgated around the same time; it applies to communications such as manufacturer publication of original trial results and letters to the editor of scientific publications in defense of public challenges.[7] More recently, this scientific exchange principle has been viewed as permitting manufacturers to provide off-label information to payer audiences, and the regulation by its terms also applies to manufacturer communications directed to lay audiences. In 1997, FDA published a guidance document identifying the criteria the agency would use in assessing continuing education to determine whether off-label information provided during those activities, when supported by industry funding, could be treated by FDA as off-label promotion.[8] A wide range of other FDA policy documents, including those issued recently on social media and other digital communications platforms, also touch on manufacturer speech issues and contribute to the complexity in this area of FDA regulation.

The agency's current stance also has roots in the Food and Drug Administration Modernization Act (FDAMA) passed by Congress in 1997.[9] Section 401 of FDAMA enabled the dissemination of peer-reviewed journal articles related to off-label indications with a confirmed commitment to filing a Supplemental New Drug Application (SNDA).[10] Section 114 enabled the sharing of health care economic information with formulary committees, managed care organizations and other large consumers of health products.[11] While FDAMA was allowed to sunset in 2007 (effectively ending the SNDA-specific provisions of Section 401), both sections continue to be touchstones for current discussion surrounding off-label communication and policymaker attempts to put forward potential solutions.

FDA continued to refine its stance on off-label communication in 2009, when it released the guidance document, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices."[12] This guidance set an updated standard for suggested reprint practices related to journal articles, scientific or medical reference texts, and clinical practice guidelines (CPGs), and was written to address the expiration of FDAMA Section 401.
In February 2014, FDA released another updated draft guidance document, "Distributing Scientific and Medical Publications on Unapproved New Uses—Recommended Practices."[13] This draft guidance further updated FDA's thoughts on best practices for distributing scientific and medical publications on unapproved new uses..

Although not intended as generally applicable policy statements, FDA has also provided perspectives on off-label information dissemination and promotion in the course of litigation. For example, a declaration submitted to a court in June 2015 by Dr. Janet Woodcock, the Director of FDA's Center for Drug Evaluation and Research (CDER), discussed the primary public health interests that are protected by current FDA approval requirements, detailed FDA's efforts to tailor its policies to advance stakeholder interests around off-label communication, and delineated why many proposed alternatives to the current regulation of off-label communication would further the latter while undermining FDA's commitment to upholding the former.[14] The FDA is widely expected to continue to refine these concepts and provide further industry guidance in the near future.

Additional Attempts to Address the Challenges Of Off-Label Communication

A number of other efforts have attempted to improve the regulatory scheme governing off-label communication. In 1997, for example, FDA launched the New Use Initiative, which was designed to accelerate the development of evidence pertaining to supplemental uses of already-approved medical products.[15] This effort would have potentially worked as a bridge for moving off-label uses to fully-approved on-label indications. The initiative experienced low uptake by manufacturers, however, likely due to continued data submission burdens and little assurance of prompt regulatory review.

In 2003, the agency attempted again to more fully address the issue of off-label information dissemination by forming an internal Unlabeled Use Task Force. The Task Force was intended to develop wider-ranging policy solutions to off-label promotion conflicts. However, it disbanded without formally releasing any proposals.

Most recently, the U.S. House of Representatives floated potential legislative fixes as part of the 21st Century Cures effort that took place in 2014-2015. The Cures Act that passed in July 2015 included one provision requiring new guidance on off-label information dissemination, and a second provision that would amend Section 114 of the FDA Modernization Act.[16] The same proposals and issues have been raised for attaching to the next iteration of prescription drug user fee legislation, expected in 2017. The future of these provisions and Senate action on similar FDA-related bills is unclear.

Litigation and the First Amendment

A clear feature of the landscape of off-label communication issues, and indeed a principal reason why past and current policies on off-label communication have been difficult to sustain, is a series of court cases examining manufacturers' First Amendment commercial free-speech rights to disseminate truthful and non-misleading information about off-label uses of approved products. The federal court of appeals decision in *United States v. Caronia (Caronia)* in 2012, although not the earliest or only case to recognize FDA-regulated manufacturers' speech rights, has been viewed as a watershed case because it explicitly rejected a government effort to criminalize accurate speech about off-label uses.[17]

Following on the heels of *Caronia*, 2015's *Amarin Pharmaceuticals Inc. v. U.S. Food and Drug Administration (Amarin)* decision by a federal district court created more pressure on the agency for new guidance.[18] Amarin Pharmaceuticals and physician plaintiffs filed a complaint alleging that the firm was being prevented, by FDA regulation, from communicating truthful and non-misleading information about the prescription drug Vascepa. The pharmaceutical company was granted preliminary relief by a district court, which gave the firm permission, based on *Caronia*, to communicate truthful and non-misleading speech via specific, court-sanctioned promotional language.[19] The suit has been stayed until March 2016 as Amarin and the Department of Justice (on behalf of FDA) work toward a potential settlement.[20]

Another important court case within the Second Circuit, *Pacira Pharmaceuticals Inc. v. the U.S. Food and Drug Administration* (*Pacira)* raised questions about the role of approved labeling.[21] Pacira sought to promote its post-surgery analgesic drug, Exparel, for uses that the FDA had alleged were unapproved, although some evidence suggested that the approved labeling could be interpreted to include these uses. The proceedings were settled in December 2015 after the FDA revised the approved labeling to make clear that the contested uses were, in fact, on-label.

Caronia, *Amarin*, and *Pacira* reflect important legal principles that constrain the government's ability to prohibit accurate off-label communications. Given the results of these cases, and in the absence of new steps on off-label communications policy, many expect further litigation as other sponsors seek to clarify the constitutional limits on the agency's authority to regulate speech in this space.

New Steps on Off-Label Communication Policy

The unsettled regulatory policy resulting from litigation and the changing evidence landscape in health care have created an environment in which further policy developments may provide more clarity and result in less litigation.

In June 2014, two citizen petitions submitted to FDA on behalf of the Medical Information Working Group (MIWG) in recent years were granted by FDA. The 2011 petition described a set of clarifications needed for off-label communications policies. It asked for an updated framework through which manufacturers could respond to unsolicited requests for information and enable scientific exchange.[22] The FDA was asked, for example, to confirm that scientific exchange included communication that clearly states that a product or use is not FDA-approved, does not claim that a product or use has been proved safe or effective, and is truthful and non-misleading when measured against available information on the product or use. The petition also asked for further clarification around manufacturer interactions with formulary committees and payers, especially in regard to the types of health care economic information they are allowed to share with such groups and the means for doing so. Finally, the petition asked for additional clarifying work around dissemination of third-party CPGs.

The 2013 petition asked for FDA to provide a comprehensive and constitutionally sound response to the 2011 petition requests, as well as a comprehensive review and modification of the regulatory scheme governing manufacturer communication to protect and promote public health.[23]

Through granting these petitions, FDA publicly agreed to revisit and review policies in order to further establish standards for truthful, non-misleading scientific communication related to drugs and devices under investigation and off-label uses of approved medical products.[24] The agency acknowledged that existing industry guidance may not be comprehensive or address major issues raised by stakeholders. Furthermore, FDA explained that as it examines its policies on off-label information dissemination, it will seek to harmonize the FDCA premarket review, labeling, and advertising provisions that apply to medical products; the important public health and safety interests served by these provisions; the usefulness of disseminating information about medical products; and constitutional considerations.

These opportunities for collaborative progress illustrate why this is an opportune time for further efforts to address the challenges in off-label communication. In addition to the legislative proposals and FDA's commitment to further action, other notable broad-based efforts such as a recent report from The Bipartisan Policy Center have suggested specific steps.[25] Despite the potential for new developments, however, these issues remain unresolved and important work remains to be done to implement an effective path forward.

Guiding Principles for Lasting Solutions

To facilitate further progress, our working group identified a set of guiding principles to inform policy options for off-label communication. While many stakeholders have strong and differing views on issues related to off-label communication, these principles are intended to reflect the concerns and objectives of a broad range of stakeholders.

Promote well-informed clinical decision-making to improve public health. The public health goal of off-label communication is to support evidence-based clinical decisions by patients, providers, and other stakeholders. Policies should keep the end users of off-label information in mind. Views may differ on how to weigh the benefits of greater dissemination of accurate information against concerns that accurate but incomplete or uncertain information may lead to worse decisions. But given the growing importance and diversity of unregulated off-label information – and given recent court decisions that affirm First Amendment protection to such information – the need to devise approaches to assure the dissemination of balanced, accurate data seems more important than ever. Off-label communication policy should be sufficiently clear to both protect and promote the public health, and to avoid chilling the dissemination of accurate and reliable information.

Policies that govern off-label communication should bolster the methods and means by which patients, caregivers, and providers are able to access the scientifically-sound evidence on off-label uses necessary for informed decision-making.

Support FDA's central role in reviewing, approving, and enforcing efficacy claims. Any policy proposed for addressing off-label communication challenges should not erode the agency's long-standing function as the expert medical product regulatory body in the United States – and ideally should strengthen it. While some areas of regulatory policy or guidance related to off-label communication may be in need of further clarification or additional stakeholder input, the fundamental authority of FDA to review and approve efficacy claims is still of utmost importance in safeguarding patients and the public health. In addition to clarifying the scope of available non-promotional pathways for dissemination of accurate off-label information, policy improvements should clarify the scope of promotional claims regarding an approved product that trigger prior FDA review.

Reduce inconsistencies across agencies' enforcement decision-making. In pursuit of more comprehensive off-label communication policy, the government agencies with enforcement authorities related to off-label communications must strive toward a more cohesive, collaborative enforcement approach. Protecting and promoting the public health require all government agencies with authority in this area to assure that enforcement actions and investigations do not have the unintended effect of adversely affecting patient care, which requires careful attention to scientific and clinical considerations. Effective regulation of off-label information dissemination also requires agencies and departments to address conflicting interpretations of the law that frustrate reasonable industry efforts to deter off-label violations.

Avoid continued cycles of litigation through greater policy clarity. The absence of clear and legally sustainable guidance on a number of key concepts related to the regulation of off-label communication has led to a series of legal challenges through which judges are left to define or revise off-label policy. Determining regulatory policy on off-label issues through serial cases in the U.S. court system does little to further address the broader communication challenges, and is an ill-suited means for formulating comprehensive off-label policy. Efforts to reform current practices should therefore seek to reduce the need for judicial action, revert policy-making activities to those with sufficient scientific expertise, and reduce the uncertainties, expense, and inefficiencies inherent in litigation.

Promote more evidence development and data submission to FDA. Off-label communications are often based upon analyses of data that are continuously accruing not only through clinical studies undertaken on medical products after they are on the market, but increasingly through data derived from routine clinical practice. Indeed many questions of clinical and economic importance, such as on comparative effectiveness, are only feasible to study through practical methods that can be applied in routine care. Such studies can also be precursors or foundations for designing more efficient and relevant randomized clinical trials. Policy solutions on off-label communications should create further incentives to develop such evidence, which can be very helpful for clinical and policy decisions even if it does not rise to the standard required for changing the product labeling. Regulatory policy should encourage product sponsors to devote resources for the collection and independent analysis of such data, and to increase the submission of findings from such studies to the FDA. This will require finding ways to advance the development of potentially useful but limited quality evidence without diminishing existing incentives to perform postmarket studies, where feasible, that can provide the high-quality evidence that meets current standards for modifying product labeling. Communication about the outcomes associated with medical products, whether off- or on-label, could be an important contributor to a broader push throughout the health care ecosystem to develop and apply real-world evidence.

Policy Options for a Path Forward

Reflecting these principles, a number of potential policy options could help address the challenges related to off-label communication. These options, which might be implemented in whole or in part, would help move away from the status quo of litigation and repeated calls for updated guidance documents. Each is intended to harmonize with both the FDA's

role in protecting public health and constitutional principles, and aims to support better evidence that patients and providers can use to make appropriate decisions about the use of approved medical products.

Immediate Administrative Responses

First, FDA should take administrative actions to clarify off-label communication policy in line with its stated commitment to address the MIWG citizen petitions. This policy step has strong support from a wide array of stakeholders, experts, and congressional leadership. While guidance with a meaningful level of detail does require significant agency resources to develop, it is a feasible lift, and previous reports and recommendations provide a relatively clear path forward. In particular, three key concepts have yet to be adequately fleshed out in guidance documents: greater clarity around the definition of "labeling;" a good working definition of "scientific exchange" as introduced in previous documents; and greater detail around the scope of "intended use." This could be accomplished in the near term and would do a great deal to improve the current off-label landscape.

Second, the FDA could increase the clarity of regulatory policy by making relevant information on its off-label policies available as a centralized, clearly structured resource. Currently, such information exists in a variety of government documents and filings that leave it to outside commentators to discern a consistent picture in this complicated policy area. To address this, FDA could develop a web page that links all existing guidance (final or otherwise) in one easy-to-access place, regularly updated and augmented by any subsequent documents as they may be released. The webpage should be stakeholder friendly, built with input from end users of off-label information, and include an adequate summary or overview of the most pertinent information related to off-label regulations.

Third, a clear process to achieve consistent enforcement of off-label communication policies should be developed across FDA and other relevant federal enforcement agencies. The enforcement environment involves much more than just FDA. As stated previously, HHS OIG, FTC, DOJ, and state attorneys general bring enforcement actions. Often, OIG or DOJ enforcement does not appear to involve close coordination with the FDA's scientific and policy experts regarding the accuracy of the communications in question and their impact on public health, potentially leading to enforcement actions and investigations that ultimately do more harm than good. In turn, different enforcement approaches can muddy the interpretation of so-called "safe harbor" provisions for communication, making it more difficult for sponsors not only to take correct steps to avoid enforcement actions, but also to have the confidence to invest in better evidence development. Greater coordination between arms of the federal government and clearer standards for when enforcement action is pursued by and between agencies would help reduce the costs of compliance with communications policy and improve the quality of information to support decision-making.

Revisions to Efficacy Claims or Product Labeling

An increasing array of decisions can benefit from evidence derived from clinical practice, and changes in off-label communication policies could enhance the development and use of such evidence. These changes would clarify how such information, particularly information that does not meet current labeling standards, could be incorporated in efficacy claims and potentially in extensions of FDA-regulated labeling. Such changes could take a variety of forms. One approach could be to maintain the current high standards for incorporating evidence within labeling itself, but with a much clearer recognition that lower levels of supporting evidence can be communicated within certain circumstances or to particular audiences – effectively allowing for a broader scope of communication that uses the labeling and additional "sanctioned" evidence as its foundation. A more extensive policy shift would involve introducing additional, clearly-delineated tiers of evidence into the product labeling: primary efficacy claims and information for an approved indication would be given the most weight and highest placement, but additional evidence with appropriate qualifications could be added to the labeling as a greater body of evidence is generated on the product's use in different contexts. This approach would not in any way alter the standards for approval of a primary indication, nor does it alter the existing standards for labeling expansion. But

it would recognize that additional evidence that does not meet those standards is being used in patient care and could benefit from ongoing review and interpretation by the FDA. This is in keeping with the agency's role in providing important information to physicians without attempting to regulate the practice of medicine.

These proposals are intended to be in line with other FDA efforts to enhance the development and use of meaningful evidence derived from real-world practice. To build on such efforts, pilot programs undertaken with the support and involvement of FDA could be accompanied by guidance on how the results of such programs could be submitted to FDA with an expedited review for purposes of labeling modification or additional efficacy-related claims. Such a pilot might use the Sentinel System, which comes with a relatively well-developed infrastructure for data cleaning and standardization and for analytic methods. Alternatively, a pilot might enable a provisional claim related to an additional indication based on limited evidence, provided that a reliable infrastructure like the Sentinel system is used to develop further evidence on the indication. Another pilot could explore a "changes-being-effected" approach commonly used to add safety information to labeling as an alternative to a more resource-intensive prior-approval SNDA process. Finally, a pilot program could focus on claims in value-based payment models, in which product sponsors are paid not based on the volume of product sold but on the basis of evidence for impact on patient health among product users. Such models likely involve knowledgeable payer and provider groups, and in any case create quite different incentives for communication and evidence development than traditional volume-based payments.

While many of these pilots seem feasible under current law, Congress may potentially need to be involved to make changes to statute or provide appropriate user fees to support clearer guidance and faster action on these issues. In any case, such efforts seem to be critical for promoting the development of more evidence on a wider range of key treatment choices, and for keeping the FDA's expertise constructively engaged in the development and use of such evidence.

Third-Party Sanctioned Communication

Although clear guidance can help reduce the burden on the agency, providing more definitive regulatory pathways and interpretations for a wider range of evidence could represent a substantial additional administrative burden for the FDA. An alternative, and one that does not have universal support within our working group, could involve an external entity charged with accrediting certain types of communication. This organization could focus its efforts on reviewing sponsor evidence and associated communications about off-label use, and approve them for broader distribution. Approval could be given within a rank, score, or grade system that confers greater weight to better evidence, and could be given contingent upon continued evidence generation and resubmission to the clearing body. For example, an off-label communication may be approved and given an initial grade or rating that sunsets within a specified number of years barring updated submission of relevant evidence. Continued off-label communication at the current evidentiary grade and after the specified date would then be subject to additional evidence development by the sponsor.

The proposed reviewing body would operate outside of FDA with FDA participation. To avoid First Amendment and other legal concerns, the body's conclusions could not bind the FDA or otherwise hinder FDA's ability to pursue enforcement action. While the reviewing body could not provide certainty to the regulated community, its recommendations could offer useful guidance to drug manufacturers.

An approach that involves an outside reviewing body might also enable FDA to advance a model that more clearly differentiates between types and levels of communication, without modifying the FDA-approved product labeling. For example, the reviewing body might treat communication around off-label use that has become standard of care in a different manner than more tailored or less-well-established evidence on an off-label indication or within a specific patient subpopulation. Such a system could potentially play a more directed and focused "peer review" alternative or supplement to the current role of peer-reviewed communications.

Such a third-party approach has precedents. In Canada, for example, the Pharmaceutical Advertising Advisory Board (PAAB) serves as an independent preclearance review agency for assessing the accuracy and evidentiary basis for promotional information on prescription, non-prescription, biologic, and homeopathic products.[26] The PAAB process works within the Canadian regulatory framework with Health Canada as an ex-officio member of board leadership, conferring "approval" of advertising materials through a logo incorporated on cleared materials. A US-based example exists in the Advertising Self-Regulatory Council (ASRC) and National Advertising Division (NAD) of the Council of Better Business Bureaus. Through self-regulation and peer-review, the ASRC and NAD were designed to avoid costly litigation between competitor companies by allowing for an independent system for adjudicating advertising claims.[27] Challengers may file complaint against a competitor with the NAD, which in turn investigates the claims under scrutiny and issues recommendations for each party; it does not issue formal or binding decisions, but instead allows for a third-party adjudication process that avoids direct legal challenges between companies.

There also may be useful lessons for a third-party off-label communication entity from the Center for Disease Control's Advisory Committee on Immunization Practices (ACIP), which develops recommendations on how and when to use vaccines within the United States.[28] With FDA as a party to committee deliberations, ACIP relies on the body of clinical evidence, sponsor labeling, and data sources to issue formal, non-binding advice for immunization best practices – including potential off-label uses of vaccines.

While these examples differ in important ways from a third-party review system for off-label materials, they illustrate features and feasibility concerns that would need to be addressed to ensure a trustworthy, collaborative, and science-based process. Any such entity will need to have participation from the FDA, and potentially other relevant agencies. The process will need to include a scientific peer-review capacity. Incentives in the form of more rapid and predictable review and action would need to be in place to encourage sponsors to develop evidence and submit communication materials. The end goal would be a process that augments the FDA's capacity to review evidence and communications based on it, does not change FDA's ability to pursue enforcement action, and allows for a potential diversity of communication types reflective of rapidly emerging evidence.

Conclusion

Stakeholders are faced with an important opportunity to move beyond the current, unsettled policy environment around off-label communication toward a system that truly works for all involved. The growing momentum from collaborative efforts tackling this issue creates a timely chance to implement a number of the proposals we have described here, lending greater clarity to the regulation of communications, increasing coordination between government agencies that oversee such regulation, and identifying new or more innovative ways to potentially ensure safe, reliable information makes it into the hands of patients, providers, and payers. However stakeholders and policymakers choose to move forward, one thing is clear: the current cycle of litigation and relative patchwork of regulations does not create a sustainable framework for continuing to generate reliable evidence on medical product use to inform patient care. We must all work together to make a better system that accomplishes this aim a reality.

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[9] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997).
[10] Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 401, 111 Stat. 2296, 2356-58 (1997).
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[12] Food and Drug Administration, *Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices*, (Jan. 1999).
[13] Food and Drug Administration, Revised Draft Guidance, *Guidance for Industry: Distributing Scientific and Medical Publications on unapproved new Uses – Recommended Practices,* (Feb. 2014).
[14] Declaration of Janet Woodcock, M.D., Amarin Pharma, Inc. v. U.S. Food & Drug Admin., No. 1:15-CV-03588-PAE (Jun. 23, 2015).
[15] *See* Food and Drug Administration, *Draft Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products; Availability*, 62 Fed. Reg. 13650 (Mar. 21, 1997); Food and Drug Administration, *Draft Guidance for Industry: FDA Approval of new Cancer Treatment Uses for Marketed Drug and Biological Products; Availability*, 62 Fed. Reg. 13659 (Mar. 21, 1997).
[16] 21st Century Cures Act, H.R. 6, 114th Cong. (1st Sess. 2015).
[17] United States v. Caronia, 703 F.3d 149 (2d Cir. 2012).
[18] Complaint, Amarin Pharma Inc. v. U.S. Food & Drug Admin., No. 15-CV-3588-PAE (S.D.N.Y. May 15, 2015).
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[20] Letter to the Hon. Paul A. Engelmayer, Amarin Pharma, Inc. v. U.S. Food and Drug Admin., No. 15-CV-03588-PAE (S.D.N.Y. Feb. 16, 2016).
[21] Complaint, Pacira Pharmaceuticals, Inc. v. U.S. Food & Drug Admin., No. 1:15-CV-07055 (Sept. 8, 2015).
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