

Points to Consider: **Truthful and Non-Misleading Product Communication**

Purpose

For the last year, BIO's Board Standing Committee on Bioethics (the "Bioethics Committee") has studied the issue of biopharmaceutical companies' truthful and non-misleading communications about their products with healthcare professionals and payers from a bioethical perspective. This work has included engagement with: external experts representing the legal and regulatory perspective on the existing Food and Drug Administration (FDA) regime; representatives of the provider and patient communities; and experts in bioethics. In the past, BIO has primarily focused our advocacy with regard to the issue of truthful and non-misleading product communication around *what* aspects of FDA's existing regulatory regime need to change, how those changes should be implemented, and to align the regime with First Amendment principles. However, to ensure that our advocacy is informed by a thoughtful, comprehensive perspective on the issue, the Bioethics Committee's study sought to identify the bioethical underpinnings of *why* change is needed in the first place and how such considerations should influence the overall framework governing such communications.

Thus, this document identifies four *Considerations* that should provide the ethical foundation for any regime governing product communication. Each of these *Considerations* has been derived from the application of relevant aspects of BIO's *Statement of Ethical Principles*.¹ Moving forward, as BIO participates in broader stakeholder discussions on this issue, BIO should ensure that our future advocacy around any changes to the legal and regulatory regime governing biopharmaceutical companies' product communication is aligned with these four bioethical *Considerations* emanating from the *Principles*.

Introduction

BIO's existing advocacy on the issue of improving the information available to payers, providers, and patients is predicated on the bioethical norm that reliable, accurate, and meaningful healthcare information should be available in a timely manner: (1) to providers and, through them, patients, at the point of clinical decision-making; and (2) to payers at the point of coverage and reimbursement determinations. Robust scientific and medical dialogue serves the widely supported healthcare *Triple Aim*: improving the patient experience of care (including quality and satisfaction); improving the health of populations; and achieving a reasonable cost of health care without compromising quality, outcomes, or access.²

The need for stakeholders to be able to access truthful and non-misleading product information is even more pressing due to the overabundance of "alternative" sources of information (e.g., social media and the general availability of health-related information on the Internet, including information specific to products that may be prescribed for seriously ill patients). Often, these sources have not been validated but are nonetheless readily available to patients. The recognition that many stakeholders rely on these sources makes

¹ BIO. 2013. *BIO Statement of Ethical Principles*. Available at: <https://www.bio.org/articles/bio-statement-ethical-principles>.

² As first described in: Berwick, D.M., T. W. Nolan, and J. Whittington. 2008. The Triple Aim: Care, health, and cost. *Health Affairs* 27(3):759-769.

it ethically important that the information be analyzed appropriately to ensure it is valid and a true representation of the medical products it discusses and that valid, truthful, and non-misleading information be communicated. In this way, stakeholders will have ready access to accurate, reliable, and meaningful information. This need will only be heightened by the drive to make medicine more personalized, which will demand more, not less, information, and especially information tailored to individual clinical circumstances.

BIO continues to engage with a diverse range of stakeholders to improve the information ecosystem for all stakeholders. This engagement includes advocating for a variety of policies, such as improving health information technology (HIT) interoperability, to ensure information can be communicated between and among providers caring for the same patient. In a number of arenas (e.g., at the federal regulatory and legislative level), BIO also has strongly supported the establishment of robust patient protections that encompass the principles of patient/provider decision making and the enforcement of such protections by states and the federal government.³ A central tenet of BIO's engagement on the issue of product communication is a focus on ensuring that all stakeholders with meaningful, truthful and non-misleading information about technologies and medicines have an equal opportunity to communicate that information for the purpose of ensuring the highest quality patient care. To achieve this goal, the ethical *Considerations* described in this paper are relevant to all parties communicating such information, not just BIO member companies. Moreover, BIO should advocate for changes to the existing legal and regulatory regime that governs biopharmaceutical companies' communication of product information so that it is consistent with these *Considerations*.

In Developing and Executing an Advocacy Strategy, BIO Should Consider the Role of Biopharmaceutical Companies in the Broader Ecosystem of Truthful and Non-Misleading Product Communication

BIO's *Statement of Ethical Principles* (the "*Principles*") identifies our positions with respect to major bioethical issues and, as such, serves to underpin our approach to the consideration of any issue from a bioethical perspective.⁴ The four *Principles* that are most relevant in the context of biopharmaceutical manufacturers' truthful and non-misleading product communication address the fundamental goal of this communication: to improve patient access to appropriate care. Specifically, these four *Principles* express BIO's commitment that:

1. "We respect the power of biotechnology and apply it for the benefit of humankind... **We support science-based regulation by government agencies of the development and use of our products to safeguard health, ensure safety, and protect the environment**" (emphasis added).

³ For example, each of the following BIO Principles documents—all of which form the basis for BIO's advocacy on patient access issues—advocates for protecting the provider/patient relationship with regard to clinical decision making: (1) our *Principles on Payment System Reform Policies* advocate that "[p]ayment reform policies must maintain flexibility for patients and their physicians to choose the therapy most appropriate for achieving the optimal quality outcome" (See BIO. 2009. Available at: <https://www.bio.org/articles/bios-principles-payment-system-reform-psr-policies>); (2) our *Principles on Universal Access to Health Care* advocate that "[i]t is both the role of the patient and physician to choose the best treatment and use the benefits of innovation appropriately" (see BIO. 2009. Available at: <https://www.bio.org/articles/bio%E2%80%99s-principles-universal-access-health-care>); and (3) our *Principles on Comparative Effectiveness* advocate that "[i]n order to achieve the best possible outcomes, providers must have the flexibility to tailor the appropriate course of treatment for each patient based on individual patient preferences and clinical circumstances" (see BIO. 2007. Available at: <https://www.bio.org/articles/bio-principles-comparative-effectiveness>).

⁴ BIO. 2013. *BIO Statement of Ethical Principles*. Available at: <https://www.bio.org/articles/bio-statement-ethical-principles>.

2. “We listen carefully to those who are concerned about the implications of biotechnology and respond to their concerns. **We help educate the public about biotechnology to enable an informed public discourse about its benefits and implications**” (emphasis added).
3. **“We will support policies that protect patient care and research integrity, as well as promote productive relationships among industry, academic, and government researchers** (emphasis added). We will not provide financial or other compensation to researchers or clinicians to influence their research results or clinical decision-making.
4. **“We support universal access to affordable, sustainable, high-quality health care for all”** (emphasis added).

These four *Principles* demand improving the information available to stakeholders at the point of healthcare decision-making to help educate stakeholders about the benefits and implications of medicines and about the value of such medicines. Additionally, these *Principles* recognize the role of science-based regulation to facilitate the communication of product information, and the importance of maintaining the integrity of the information ecosystem through addressing conflicts of interest (COI). In short, through BIO’s broader advocacy and through the Bioethics Committee’s recent study, we have identified four primary *Considerations* that can foster an ecosystem that supports these *Bioethical Principles*:

- All parties communicating product information should ensure timely, truthful and non-misleading information—including, but not limited to, the clinical and other information contained in a product’s FDA labeling—is available to all relevant stakeholders;
- Timely, efficient mechanisms should be in place to ensure the quality of the truthful and non-misleading information that is communicated;
- Any regime governing truthful and non-misleading communication should take into account whether such information is meaningful in the context of patient care; and
- COI should be assessed through a common mechanism, not through stakeholder-specific means, and mechanisms to address COI should be built from the existing work on this subject.

Each of these *Considerations* is addressed in turn in the balance of this document. In developing and executing an advocacy strategy to address the tension between the current ecosystem of biopharmaceutical companies’ communication and the need for truthful and non-misleading communications, BIO should take into account these *Considerations*.

Timely Access: As a crucial aspect of an efficient, effective healthcare system, all relevant parties should ensure that truthful and non-misleading product information—including, but not limited to, the clinical and other information contained in a product’s FDA-approved labeling—is available at the point of: (1) patient/provider decision-making; and (2) payer determinations with regard to coverage and reimbursement. This should include relevant, meaningful, and quality information communicated by biopharmaceutical companies.

The stakeholders making decisions about biopharmaceutical products do not always have timely access to all of the relevant truthful and non-misleading product information to

facilitate well-informed clinical decision-making. This reality can detract from a central tenet of an efficient, effective healthcare system: getting the right patients access to the right treatment interventions at the right time. The existing regulatory regime governing truthful and non-misleading product communication is a prominent contributor to the fact that stakeholders must make decisions with regard to the use of medicines with incomplete information—though it is not the only factor (e.g., technological hurdles, such as the lack of integrated, interoperable data systems, also hinder the availability of relevant data at the point of decision-making).

Although biopharmaceutical companies often have the most comprehensive, up-to-date, quality and meaningful information about their products, their communications are more restricted as compared with those of other stakeholders. This is the result of FDA's current interpretation of the statutory provisions it deems applicable to biopharmaceutical companies' proactive communications about information related to an approved product.⁵ FDA's interpretation of existing law, lack of clear and comprehensive formal guidance on this matter, and an inability to provide timely feedback to biopharmaceutical companies create an environment that is generally viewed by biopharmaceutical companies as limiting or restricting their proactive communication of truthful and non-misleading scientific, medical, or pharmacoeconomic information about an approved product. Meanwhile, other stakeholders, including academia and insurers, are not bound by such limitations. Furthermore, there appear to be virtually no limitations on the information that can be obtained from the largely unregulated "wild west" of the Internet.

FDA has provided draft guidance with respect to biopharmaceutical companies' communication of truthful and non-misleading information in *response* to unsolicited inquiries, which includes significant restrictions on how a company may respond to such inquiries. Specifically, in 2011 draft guidance, FDA "recognizes that [biopharmaceutical companies] are capable of responding to requests about their own named products in a truthful, non-misleading, and accurate manner"⁶ and proposes standards for responding. The draft guidance notes that if a biopharmaceutical company "responds to unsolicited requests for off-label information in the manner described in this draft guidance, FDA does not intend to use such responses as evidence of the firm's intent that the product be used for an unapproved or un-cleared use."⁷ However, the communications parameters established in the draft guidance suggest that biopharmaceutical companies may not be able to communicate truthful and non-misleading information in ways that are similar to how other stakeholders communicate, even when responding to unsolicited information requests. For example, the information a biopharmaceutical company provides in response to an unsolicited request: "should be scientific in tone and presentation," "should be tailored to answer only the specific question(s) asked," and may "be provided only to the individual making the request directly to the [biopharmaceutical company]."⁸ Thus, even in this circumstance—i.e., a direct request for information—biopharmaceutical companies'

⁵ The Second Circuit Court of Appeals' noted in *U.S. v. Caronia* that, based on FDA's interpretation, "the government has treated promotional speech as more than merely evidence of a drug's intended use – it has construed the FDCA to prohibit promotional speech as misbranding itself" (*U.S. v. Caronia*, 703 F.3d 149, 155 (2d Cir. 2012)). The same opinion—in rejecting the validity of this interpretation on First Amendment grounds—recognized that "[t]he government has repeatedly prosecuted – and obtained convictions against – pharmaceutical companies and their representatives for misbranding based on their off-label promotion." *Id.* at 154.

⁶ FDA. 2011. *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices Draft Guidance*, lines 83-85, available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm285145.pdf>.

⁷ *Id.* at lines 92-94.

⁸ *Id.* at lines 281-282, 240-241, 237-238.

communication of truthful and non-misleading information appears to be more limited than communication by any other healthcare sector stakeholder.

This regulatory regime has created an environment that, because of the restriction to only certain types of stakeholder communications, hinders valuable medical and scientific dialogue, a fact that has been noted by many. For example, in testimony before the House Committee on Energy and Commerce, Subcommittee on Health, Gregory Schimizzi, M.D., Cofounder of Carolina Arthritis Associates, on behalf of the Alliance for Specialty Medicine, noted that “[t]he FDA does not allow pharmaceutical companies to actively distribute key clinical information, even if it is related to the on-label indication, unless it is explicitly referenced in the package insert of that product. By limiting the sharing of information, physicians are hampered in their ability to gain all of the firm scientific rationale and medical evidence needed to treat patients.”⁹

The consequences of this regulatory regime not only limit the information available to providers and payers at the time that a treatment becomes available on the market, but extend further. Knowledge about a therapy’s benefits and risks, the impact on downstream treatment decisions and broader utilization of healthcare services, and the effectiveness for certain patient subpopulations evolve over time. As described in a recently released White Paper on the emerging benefits of oncology therapies, “FDA approval marks the ‘starting point’ for additional study of [a] therapy, followed by the development of a larger body of evidence to help us understand the full value of the treatment and, more importantly, to help clinicians understand how best to use available therapies when treating their patients.”¹⁰ This sentiment was reiterated by US House of Representatives Committee on Energy and Commerce Subcommittee on Health Chairman Pitts in his opening remarks at the above-referenced hearing, in which he noted that “[t]reatment in the real world also brings out additional information on safety and efficacy, and ensuring that this knowledge is shared widely among providers, payers, patients and researchers is critical. As a result, the ability of patients, physicians *and biopharmaceutical companies* to communicate effectively is so important for the future of cures in this country” (emphasis added).¹¹

Biopharmaceutical companies often are a major contributor to this ongoing data gathering and analysis, yet are hampered in their ability to communicate meaningful advances in understanding in a timely manner, which, in turn, can significantly impede the efficiency and effectiveness of the information ecosystem as a whole. Improving this ecosystem will help realize the BIO bioethical *Principles* that are the focus of these *Considerations* by: (1) advocating for legal and regulatory standards that are science-based without inappropriately restricting information that can aid patient/provider decision-making; (2) establishing the benefits and implications of a specific medicine for a specific patient—with the understanding that patients can have perspectives on benefit/risk considerations that are distinct from those held by other stakeholders—to improve the efficiency and effectiveness of healthcare decisions; (3) enabling more informed evaluations

⁹ Testimony of Gregory Schimizzi, M.D., before the House of Representatives Subcommittee on Health, Committee on Energy and Commerce (July 22, 2014), Hearing on 21st Century Cures: Examining Barriers to Ongoing Evidence Development and Communication, available at: <http://docs.house.gov/meetings/IF/IF14/20140722/102524/HHRG-113-IF14-Wstate-SchimizziG-20140722.pdf>.

¹⁰ Sweeney, N. and T. F. Goss. 2015 (May). The Value of Innovation in Oncology: Recognizing Emerging Benefits Over Time. *Boston Healthcare*, available at: http://www.phrma.org/sites/default/files/pdf/bha_value_of_cancer_innovation-whitepaper.pdf.

¹¹ Prepared Statement before the House of Representatives Subcommittee on Health, Committee on Energy and Commerce (July 22, 2014), Hearing on 21st Century Cures: Examining Barriers to Ongoing Evidence Development and Communication, 113th Cong. Serial No. 113-163, available at: <http://www.gpo.gov/fdsys/pkg/CHRG-113hhrg93247/html/CHRG-113hhrg93247.htm>.

of the value of medicines; (4) promoting productive relationships among stakeholders working to optimize patient health outcomes; and (5) ensuring that patients receive high quality care, a decision that depends on a timely assessment of truthful and non-misleading information with regard to a specific intervention.

Quality Information: No matter the source, it is critical that information communicated about medicines is of high quality. Thus, advocacy to expand biopharmaceutical companies' ability to communicate truthful and non-misleading information about their therapies should consider the standards for evaluating the quality of the information, how and by whom the quality will be assessed, and how that assessment will be incorporated into the information communicated.

In addition to stakeholders'—including biopharmaceutical companies'—responsibility to provide timely truthful and non-misleading information to healthcare decision makers, it is also critical that this information is of high quality. The standards by which the quality of the information to be communicated is assessed must be transparent, and the process for assessment should not be so burdensome or time-consuming that it hinders the timely provision of truthful and non-misleading information. An assessment of the quality of information also requires an evaluation of the context in which the information was collected (or derived) and analyzed (i.e., quality cannot be determined based on a single indicator or without an understanding of how data were collected and from what sources, how the data were analyzed, and what level of accuracy the conclusions of such data collection represent). Moreover, quality should be assessed distinct from the source of the information, which may not be a reliable proxy for its quality. As just one example, consider a 2012 study by University of California, San Diego, in which researchers assessed 98 of the top English-language websites on celiac disease, published by academic, commercial, nonprofit, and other professional sources, for accuracy, comprehensiveness, transparency, and reading grade level.¹² The researchers found that the type of website publisher did not predict website accuracy, comprehensiveness, or the overall quality of information. In fact, they found that academic websites were significantly less transparent ($P = .005$) than commercial websites in attributing authorship, timeliness of information, and sources of information. Although the quality of information is significantly variable, the information nevertheless has great potential to be used for healthcare decision-making.

Stakeholders are bombarded with information of questionable quality from a myriad of other sources. Patients, providers, payers, and others need timely, truthful and non-misleading information that is of high quality. Biopharmaceutical companies, along with all other stakeholders, are responsible for ensuring that information they provide meets that standard.

Under the existing legal and regulatory system, FDA is the primary arbiter of quality information, and FDA reflects such determinations in decisions regarding information included in a product's label. Specifically, if the *Agency* determines that the product information the biopharmaceutical manufacturer has provided as part of the regulatory

¹² McNally, S. L., M. C. Donohue, K. P. Newton, S. P. Ogletree, K. K. Conner, S. E. Ingegneri, and M.F. Kagnoff. 2012. Can consumers trust web-based information about celiac disease? Accuracy, comprehensiveness, transparency, and readability of information on the internet. *Interactive Journal of Medical Research* 1(1):e1.

approval package has been substantiated by sufficient scientific evidence and is important to clinical decision making, the information is considered inherently “of high quality,” and is included on a therapy’s label.¹³

The *Bioethical Principles*, however, do not support limiting the exchange of quality information to that permitted by the current regulatory scheme. Rather, sources of information outside a product's labeling also can provide quality, truthful and non-misleading information critical to the delivery of care or the assessment of the value of that care (e.g., in the case of information about rare disease therapies, where alternative statistical models may provide sufficient study power with smaller sample size and/or with regard to the impact of a therapy—including relevant pharmacoeconomic data—on a patient subpopulation). We are not suggesting that the FDA be ignored in helping to guide the flow of quality information. However, the *Principles* demand that the regulatory mechanism recognize the diversity of quality information that may be available, even if additional context is needed to ensure an appropriate understanding of the information. Any such mechanism should be sufficiently flexible to adapt to and evaluate the variety of information sources in a timely manner, and capable of accurately assessing the quality of that information.

Meaningful Information: Advocacy should consider the scope of the responsibility of biopharmaceutical companies to provide healthcare providers and payers with information concerning a product. That scope might be defined by the information that is considered meaningful to the responsible use of therapies or medicines. Advocacy efforts should consider the standards for evaluating the meaningfulness of the information to be shared, how and by whom that meaningfulness will be assessed, and how that assessment will be incorporated into the information communicated.

All stakeholders should consider the meaningfulness of product information in determining whether and how to communicate it. Information can be truthful and non-misleading without regard to its meaningfulness. However, too much information sharing—especially if not meaningful—can do a disservice. Thus, the meaningfulness of information is critical to consider in the context of BIO’s advocacy on this issue, in particular since the broader goal of this advocacy is to ensure that all healthcare stakeholders have timely access to the information they need to make appropriate healthcare decisions. There is a dimension of meaningfulness that can depend on the audience, and biopharmaceutical companies must be aware of the impact of the substance and format of information on its meaningfulness. In addition, meaningfulness may depend to a greater degree on how the information can/will be utilized.

For example, information about a therapy may be considered meaningful if: (1) the information can be extrapolated to address how the therapy can/should be used in the context of an individual patient’s clinical circumstances; (2) the information indicates where in the prevention, diagnosis, and/or treatment process the therapy is best utilized; and (3) the information indicates the limitations of the use of the therapy. The more clearly a stakeholder—including a biopharmaceutical company—can define what makes product

¹³ Under the existing regulatory regimen, the distinction between on- and off-label with regard to what FDA deems as permissible product communication is stark: as described in an earlier section, biopharmaceutical manufacturers potentially face significant barriers to communicating information outside of the four corners of the FDA-approved labeling, even though such information may be wholly truthful and non-misleading.

information meaningful in a particular circumstance, the more likely that the information can contribute positively to efficient, effective healthcare decision-making.

Not all product information collected by a stakeholder is necessarily relevant or appropriate for communication. Thus, the meaningfulness standard can focus all stakeholders on the relevance of the information, rather than quantity of information communicated or the frequency of the communications. Similarly, a focus on the meaningfulness of truthful and non-misleading information means that all stakeholder resources are utilized efficiently and contribute to ensuring the most relevant information is available throughout the healthcare decision making process.¹⁴

Clarity with Regard to Conflicts of Interest: Potential conflicts of interest, with respect to truthful and non-misleading product communication, are not confined to a single stakeholder group, but may exist across the spectrum of healthcare sector stakeholders. A systematic mechanism for providing adequate context for information communicated by any stakeholder is a crucial part of advocacy to ensure appropriate communications from all stakeholders, with the goal of promoting the best outcome for patients.

In considering how to improve the existing environment to facilitate timely, truthful and non-misleading communication about biopharmaceutical products, it is important to identify whether sufficient mechanisms are already in place to address the potential for COI. If not, BIO should work collaboratively with stakeholders, including regulators, to identify COI protocols that are broadly applicable and not overly burdensome such that they would inhibit the timely communication of truthful and non-misleading product information. COI, or perceived COI, can negatively impact how truthful and non-misleading information is utilized, or whether it is utilized at all. Thus, addressing COI comprehensively can preserve the utility of this information and facilitate its appropriate use in clinical decision making and/or coverage and reimbursement determinations. Key to accomplishing this is establishing a transparent process that identifies, discloses, and mitigates COI no matter its source. Disclosures should take into account the literacy level of all potential audiences, as well as clearly identify the potential impact of identified COI on the interpretations of the data. The COI process also is an important opportunity to identify the checks and balances in place throughout the process of communicating truthful and non-misleading information, including through the review of information quality and meaningfulness. BIO also should consider whether minimum standards for the COI review and disclosure process across stakeholders are necessary, what standards would be most appropriate, and whether standardization can improve the transparency and comprehensiveness of these processes across the board.

Conclusion

¹⁴ By focusing on the "meaningfulness" of information, we do not mean to relieve the responsibility of biopharmaceutical companies to provide timely, truthful and non-misleading information that is of high quality. Companies are responsible to present data in a balanced, transparent manner so as to support optimal decision making for use of their medicines. Presentations should not exclude information specifically because it might not promote the sponsor's interests. The specifics regarding analyses, tests, missing data, inclusions/exclusions, and endpoints and their specificity should be presented where important to understanding the data and should be available upon request to those interested.

BIO's *Statement of Ethical Principles* identifies our organization's commitments with respect to the socially responsible development and use of biotechnology to help save or improve lives. These commitments include, but are not limited to: (1) supporting science-based regulatory standards to govern the use of biopharmaceuticals; (2) helping to educate the public about biotechnology to enable an informed public discourse about its benefits and implications; (3) facilitating productive relationships among stakeholders to achieve the goal of optimizing patient care for individual patients; and (4) supporting universal access to high-quality health care for all, among other commitments. Applying these *Principles* in the context of timely, truthful and non-misleading product communication, BIO identifies four *Considerations* that can help to operationalize these *Principles*:

- All parties communicating product information should ensure that timely, truthful and non-misleading information—including, but not limited to, the clinical and other information contained in a product's FDA-approved labeling—is available to all relevant stakeholders;
- Timely, efficient mechanisms must be in place to ensure the quality of the truthful and non-misleading information that is communicated;
- Any regime governing truthful and non-misleading communication should take into account whether such information is meaningful in the context of patient care; and
- COI should be assessed through a common mechanism, not through stakeholder-specific means, and mechanisms to address COI should be built from the existing work on this subject.

These four *Considerations* should guide a regime that will enable stakeholders to make well-informed decisions based on the individual clinical circumstances of each patient. In doing so, such a regime will be better able to promote patient access to the most appropriate technologies for them and contribute to increasing the efficiency and effectiveness of the healthcare system. This document is a companion to, and should be used in conjunction with, the PhRMA-BIO Principles on Responsible Sharing of Truthful and Non-Misleading Information about Medicines with Health Care Professionals, available at https://www.bio.org/sites/default/files/PrinciplesReport_FINAL.pdf