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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products; Request for Comments, Docket No. FDA-2016-N-1149, 81 Fed. Reg. 60,299 (Sept. 1, 2016)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (“PhRMA”) appreciates the opportunity to comment in response to FDA’s notification of public hearing about manufacturer communications regarding unapproved uses of approved or cleared medical products (“FDA hearing notice”) and FDA’s Memorandum titled “Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products” (the “First Amendment Memorandum”).¹ We also appreciated the opportunity to testify at FDA’s Public Meeting about these issues on November 9 and 10, 2016. PhRMA is a voluntary, non-profit association that represents the country’s leading pharmaceutical research and biotechnology companies. PhRMA members are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA’s member companies have invested more than half a trillion dollars in the search for new treatments and cures, including an estimated \$58.8 billion in 2015 alone.

As an initial matter, PhRMA appreciates that FDA in January 2017 issued separate draft guidance documents addressing manufacturer communications with payors, formulary committees, and similar entities, and manufacturer communications with healthcare professionals that are consistent with the FDA-approved labeling.² In those draft guidance documents, FDA proposes to allow communications based on sound science, subject to disclosure of contextual information and limitations to help ensure that the communications are truthful and non-misleading for their intended audiences. FDA also appropriately acknowledges in those documents that the standards for substantiation of communications should not be

¹ 81 Fed. Reg. 60299 (Sept. 1, 2016); FDA, Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (Jan. 2017) (“First Amendment Memorandum”).

² See FDA, Draft Guidance, Drug and Device Manufacturer Communication with Payors, Formulary Committees, and Similar Entities—Questions and Answers (Jan. 2017); FDA, Draft Guidance, Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers (Jan. 2017).

coextensive with the standard for approving medical products for use. PhRMA is simultaneously submitting separate comments in response to each of those draft guidance documents, in which we offer suggestions for enhancement, but which are generally supportive of the FDA's overarching approach to balancing the interests of the speaker with the FDA's regulatory interests in those contexts.

However, we have more deep-rooted concerns with the FDA's public hearing notice and First Amendment Memorandum, to which this comment letter specifically relates. Specifically, PhRMA believes that the First Amendment Memorandum inappropriately proposes to restrict important speech about unapproved uses of medical products that could be beneficial to both healthcare professionals and the patients that they serve. The First Amendment permits FDA to restrict speech only as a last resort, and places the burden squarely on FDA to support any restrictions on speech. The positions FDA takes in the First Amendment Memorandum do not meet this burden, as there are clearly less-restrictive means to address the FDA's regulatory concerns with respect to communications about unapproved uses of medical products than the current approach.

In particular, in July 2016, PhRMA and the Biotechnology Innovation Organization ("BIO") jointly published their "Principles on Responsible Sharing of Truthful and Non-Misleading Information about Medicines with Health Care Professionals and Payers" ("PhRMA-BIO Principles").³ The PhRMA-BIO Principles set forth important concepts that PhRMA strongly endorses with regard to manufacturer communications with healthcare professionals and payors about unapproved uses. The PhRMA-BIO Principles strike the constitutionally required balance between FDA's role in evaluating the safety and efficacy of new medicines and new uses of previously-approved medicines, and the needs of patients for their insurers and healthcare professionals to be fully educated about available treatment options. The PhRMA-BIO Principles achieve this balance by focusing on three core concepts:

- (1) Communications should be based on analyses using scientifically- and statistically-sound methodologies.
- (2) Communications should clearly disclose appropriate contextual information to ensure that the recipient has all of the material necessary to make an informed assessment about the quality of the information presented.
- (3) Communications should accurately represent the data on which they are based and should be tailored to the sophistication level of the intended audience.

At a minimum, FDA should allow manufacturers to communicate, subject to the three above concepts, about unapproved uses of FDA-approved medicines that are medically accepted. As used in this comment letter, medically accepted uses are those supported by: (a) citations in one or more of the statutory compendia used for Medicare or Medicaid payment purposes ("CMS-recognized compendia"); (b) clinical practice guidelines issued by national medical

³ See *infra* App. A.

societies; (c) Medicare coverage manuals, such as the Medicare Benefit Policy Manual; or (d) clinical research that appears in peer-reviewed medical literature appearing in the regular edition of at least one of the publications listed in Chapter 15, Section 50.4.5(C) of the Medicare Benefit Policy Manual and satisfies the criteria set forth in such Section.⁴

The concepts set forth in the PhRMA-BIO Principles help not only to ensure that communications are truthful and non-misleading, but also that each of FDA's asserted regulatory interests is protected. PhRMA urges FDA to adopt a Principles-based approach in reforming its regulatory framework for manufacturer communications with healthcare professionals and payors about medically accepted unapproved uses. This approach, which would incorporate the three key safeguards described above, adequately preserves FDA's legitimate interests without infringing the First Amendment rights of pharmaceutical manufacturers. It is thus a less restrictive alternative to the current framework.

As discussed above, the safeguards proposed in the PhRMA-BIO Principles should govern all proactive manufacturer communications with sophisticated audiences, including healthcare professionals, payors and population health decision-makers.⁵ We understand that the First Amendment Memorandum carves out communications in the setting of more conventional scientific exchange, including responses to unsolicited requests and dissemination of reprints of textbooks, medical journal articles, and other reference materials. Consequently, the framework we propose in this comment letter should not apply to: (1) the distribution of reprints of medical journal articles and medical or scientific reference publications on unapproved uses of FDA-approved products;⁶ (2) responses to unsolicited requests;⁷ or (3) other forms of scientific exchange, such as proactive communications at scientific conferences. FDA has already developed a framework for regulating scientific and medical publications and responses to unsolicited requests, and we have previously provided our comments on the operative FDA guidance documents governing these topics.⁸

⁴ This definition incorporates statutory definitions of medical acceptance from the Medicare and Medicaid statutes. See 42 U.S.C. §§ 1395x(t)(2)(B), 1396r-8(k)(6).

⁵ As used in this comment letter, a "population health decision maker" is any individual or group who makes coverage and reimbursement decisions at a level higher than the individual.

⁶ FDA, 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. 2009), available at <https://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm>. PhRMA's positions with respect to the distribution of reprints can be found in Principle Nine of the PhRMA-BIO Principles.

⁷ FDA, Draft Guidance, Responding to Unsolicited Request for Off-Label Information About Prescription Drugs and Medical Devices (Dec. 2011), available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf?source=govdelivery>.

⁸ See PhRMA, Comment Letter responding to FDA, Revised Draft Guidance, Distributing Scientific and Medical Publications on Unapproved New Uses (submitted May 1, 2014), available at <http://phrma-docs.phrma.org/sites/default/files/pdf/Comments-FDA-Reprints-Guidance-5-1-14.pdf>.

Our comments below are directed to proactive manufacturer communications regarding medically accepted unapproved uses that meet the standards we have described above. The remainder of this comment letter can be summarized as follows:

- Section I describes the First Amendment principles that limit FDA’s ability to restrict manufacturer communications about unapproved uses.
- Section II describes PhRMA’s proposed approach to such communications, drawing on the core concepts set forth in the PhRMA-BIO Principles and as described above.
- Section III demonstrates that PhRMA’s proposed approach adequately serves FDA’s legitimate interests without unconstitutionally restricting manufacturers’ protected speech.
 - Sections III(A) and (B) set forth PhRMA’s agreement with FDA that broader communications with healthcare providers and payors will result in better informed clinical decision-making and will further scientific understanding and research.
 - Sections III(C)–(F) describe how PhRMA’s proposed safeguards will advance FDA’s interests in the continued development of robust scientific data, ensuring accurate and informative product labeling, protecting against false or misleading communications, preventing public harm, and preserving incentives for clinical trial participant protection and participation.
 - Section III(G) explains how PhRMA’s proposed framework furthers FDA’s interest in protecting innovation incentives and the development of products for underserved patient populations, and the narrow circumstance in which a speech restriction could be justified to preserve a period of regulatory exclusivity.
- Section IV responds to FDA’s analysis of less restrictive alternatives. While PhRMA agrees with FDA’s analysis of some of those alternatives, several of them in our view—including our recommendation of a Principles-based framework that requires contextual disclosure, scientific and statistically sound methodologies, and a sophisticated audience—would be less-restrictive alternatives required by the First Amendment case law.
- Section V proposes specific revisions to existing FDA regulations to implement PhRMA’s Principles-based proposal.

I. The First Amendment Prohibits Overly Restrictive FDA Regulation of Manufacturers’ Communications Regarding Unapproved Uses

PhRMA recognizes the importance of FDA’s regulatory processes for approving new medicines and new indications for previously approved medicines to maintain the safety and efficacy standards that keep patients safe. At the same time, we also recognize the critical need of patients for healthcare professionals and payors to be well informed about the benefits and risks of all available uses of medicines. Physicians must be able to exercise their independent medical judgment in determining the appropriate treatment option for their patients, including, when appropriate, to prescribe an FDA-approved drug for an unapproved use. Similarly, payors and other population health decision-makers must be fully informed in making their judgments about products that are appropriate for coverage and payment. PhRMA believes that its

members can serve an important public health role and advance the interests of patients by providing truthful, non-misleading information to these healthcare professionals and population health decision-makers about their medicines. Any appropriate regulation by FDA in this area thus requires careful balancing of multiple interests.

The Constitution’s protection of an open and robust exchange of ideas—principles that are central to the meaning and purpose of the First Amendment—tilts this balance strongly in favor of the speaker and accordingly limits FDA’s ability to restrict truthful and non-misleading communication. PhRMA respectfully submits that FDA must carefully abide by these limitations in reviewing and reforming its regulations, policies, and enforcement priorities regarding manufacturers’ communications with healthcare professionals and payors about unapproved uses.

A. Restrictions Would Be Subject to Heightened Scrutiny and Would Fail

In *Sorrell v. IMS Health Inc.*, the Supreme Court reaffirmed that “[s]peech in aid of pharmaceutical marketing . . . is a form of expression protected by the Free Speech Clause of the First Amendment.”⁹ The First Amendment, the Court observed, serves a particularly critical function “in the fields of medicine and public health, where information can save lives.”¹⁰

Overly-restrictive FDA regulation of biopharmaceutical companies’ communications with healthcare professionals about unapproved uses not only harms patient interests in physician education, but also would be subject to heightened scrutiny under judicial review and would not survive that test. In *Sorrell*, the Supreme Court applied “heightened judicial scrutiny” to strike down a Vermont law that burdened pharmaceutical manufacturers’ communications with healthcare professionals about their medicines.¹¹ Heightened scrutiny applied, the Court explained, because the law imposed both “content- and speaker-based restrictions” on protected speech.¹² In other words, the law “impose[d] a burden based on the content of speech and the identity of the speaker.”¹³

FDA restrictions on manufacturers’ communications with healthcare professionals about unapproved uses likewise trigger heightened scrutiny because they are speaker-based and content-based. Such restrictions are speaker-based because other individuals and entities may engage in the same communications with the same audiences without violating the law. And the restrictions are content-based because they would penalize companies for disseminating information about unapproved uses. Following *Sorrell*, the Second Circuit in *United States v. Caronia* thus held that “[t]he government’s construction of the [Food Drug & Cosmetic Act’s

⁹ 564 U.S. 552, 557 (2011).

¹⁰ *Id.* at 566.

¹¹ *Id.* at 565.

¹² *Id.* at 563.

¹³ *Id.* at 567; *accord id.* at 564 (observing that the law “disfavor[ed] marketing, that is, speech with a particular content,” and “disfavor[ed] specific speakers, namely pharmaceutical manufacturers”).

(‘FDCA’) misbranding provisions to prohibit and criminalize the promotion of off-label drug use by pharmaceutical manufacturers is content- and speaker-based, and, therefore, subject to heightened scrutiny.”¹⁴

Against this backdrop, any notion that FDA restrictions on manufacturer communications about unapproved uses would not trigger heightened judicial scrutiny lacks merit. Citing the dissents in both *Sorrell* and *Caronia*, FDA asserts that its restrictions on such speech are “necessarily both speaker- and content-based as part of reasonable government regulation of particular industries in the interest of greater public good.”¹⁵ But a dissent is not the law. The majority in *Sorrell* held that speaker- and content-based restrictions on protected speech trigger heightened scrutiny, and the majority in *Caronia* held that such scrutiny therefore applies to restrictions on manufacturer communications about unapproved uses. Regardless of whether FDA believes that the federal courts’ conclusion “makes sense” or is “appropriate,”¹⁶ it is the law, and FDA’s regulations must be structured consistently with that level of scrutiny.

The application of heightened scrutiny leads to a virtual presumption of unconstitutionality for content-based restrictions of truthful and non-misleading speech. As the *Sorrell* Court noted, “[i]n the ordinary case it is all but dispositive to conclude that a law is content-based and, in practice, viewpoint discriminatory.”¹⁷ Likewise, in *Reed v. Town of Gilbert*, the Court reiterated that “[c]ontent-based laws—those that target speech based on its communicative content—are presumptively unconstitutional and may be justified only if the government proves that they are narrowly tailored to serve compelling state interests.”¹⁸ The First Amendment Memorandum does not satisfy the standards of *Sorrell* and *Reed*.

B. Speech Restrictions Also Would Fail Intermediate Scrutiny and Would Harm Patients By Restricting Availability of Information About Medically-Accepted Unapproved Uses of Medicines

Even analyzed under commercial speech doctrine, burdensome FDA restrictions on pharmaceutical manufacturers’ truthful and non-misleading communications about unapproved uses would fail, because the balance required when evaluating such restrictions similarly favors a free flow of truthful and non-misleading scientific information.

¹⁴ 703 F.3d 149, 164-65 (2d Cir. 2012).

¹⁵ First Amendment Memorandum, 24-25 (citing *Sorrell*, 564 U.S. at 582-92 (Breyer, J., dissenting); *Caronia*, 703 F.3d at 180-81 (Livingston, J., dissenting)).

¹⁶ First Amendment Memorandum, at 25.

¹⁷ *Sorrell*, 564 U.S. at 571.

¹⁸ 135 S. Ct. 2218, 2226 (2015); *see also id.* at 2227 (“Government regulation of speech is content based if a law applies to particular speech because of the topic discussed or the idea or message expressed.” (citations omitted) (citing *Sorrell*, 564 U.S. at 563)).

Courts have long expressed skepticism about regulation of mixed commercial and scientific speech.¹⁹ At a minimum, then, the government must show that a restriction on commercial speech directly advances a substantial government interest that could not be served as well by a more limited restriction.²⁰ This standard offers significant protection, particularly insofar as it disfavors paternalistic regulations targeted against particular speakers or messages.²¹

In *Caronia*, the Second Circuit held that a misbranding conviction based solely on a pharmaceutical sales representative's truthful and non-misleading speech about an unapproved use would fail First Amendment scrutiny even under the *Central Hudson* test. Because "physicians can prescribe, and patients can use" FDA-approved drugs for unapproved uses, the court explained, restrictions on manufacturers' speech about such uses would not "directly further the government's goals."²² The court further reasoned that such a restriction "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information" and "could inhibit, to the public's detriment, informed and intelligent treatment decisions."²³

The paternalism criticized in *Caronia* has long been regarded as an insufficient—and, indeed, illegitimate—justification for restricting truthful speech.²⁴

In its analysis of the risks that communications about unapproved uses to healthcare professionals would pose, FDA's First Amendment Memorandum echoes the same flawed paternalistic view that the courts have long rejected. On one hand, the Agency acknowledges that "[s]cientific or medical information regarding unapproved uses of products may help health

¹⁹ See *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d at 51, 62 ("The resolution of this question is not an easy one, as the communications present one of those 'complex mixtures of commercial and non-commercial elements.'").

²⁰ *Cent. Hudson Gas & Elec. Corp. v. Public Serv. Comm'n of N.Y.*, 447 U.S. 557 (1980).

²¹ See *Thompson v. W. States Med. Ctr.*, 535 U.S. 357 (2002) (striking down federal statute prohibiting pharmacy compounding advertising under *Central Hudson* commercial speech test); *Va. State Bd. Of Pharm. v. Va. Citizens Consumer Council*, 425 U.S. 748 (1976) (striking down state statute prohibiting pharmacy advertising of prescription drug prices).

²² *Caronia*, 703 F.3d at 166.

²³ *Id.*

²⁴ See, e.g., *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484, 503 (1996) ("[B]ans against truthful, non-misleading commercial speech . . . usually rest solely on the offensive assumption that the public will respond 'irrationally' to the truth. . . . The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good." (quoting *Linmark Assocs., Inc. v. Willingboro Twp.*, 431 U.S. 85, 96 (1977))); *Va. State Bd. Of Pharm.*, 425 U.S. at 770 (criticizing government's "highly paternalistic approach" to free flow of truthful, non-misleading information about pharmaceutical products). FDA's argument that *Caronia* is no longer good law—or that the Second Circuit might reconsider it—in light of a single study about "unapproved uses and adverse drug events" is meritless. First Amendment Memorandum at 23-24 (discussing Tewodros Eguale et al., *Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population*, 176 *JAMA Intern Med.* 55 (Jan. 2016)). Similar studies critical of unapproved uses have existed for many years. And the Second Circuit did not reason that unapproved uses never lead to adverse drug events, but rather that such uses are lawful and therefore may be discussed truthfully by pharmaceutical manufacturers and others alike.

care providers make better decisions regarding a patient”²⁵ On the other hand, however, FDA repeatedly calls into question the ability of trained healthcare professionals to make informed and intelligent treatment decisions for patients based on such truthful, non-misleading information.²⁶

Such paternalistic views—particularly with respect to the ability of physicians to assess information about treatment options for patients—do not and cannot justify restricting speech. As the *Sorrell* Court concluded, “[t]he fear that [physicians] would make bad decisions if given truthful information [about FDA-approved prescription drugs] cannot justify content-based burdens on speech.”²⁷

Following *Caronia*, the district court in *Amarin Pharma, Inc. v. FDA* held: “Where the speech at issue consists of truthful and non-misleading speech promoting the off-label use of an FDA-approved drug, such speech, under *Caronia*, cannot be the act upon which an action for misbranding is based.”²⁸ The court rejected FDA’s argument—repeated in the Agency’s First Amendment Memorandum²⁹—that the government may use speech as “evidence of intent.”³⁰ As the court explained, “the proposition that speech can be admissible in evidence to prove intent or motive in a criminal case is beside the point here,” because FDA’s restrictions on manufacturer communications about unapproved uses “take[] aim at truthful, non-misleading speech,” and not any other “actus reus.”³¹ This case is thus distinguishable from *Wisconsin v. Mitchell*³² and *Whitaker v. Thompson*,³³ where speech was introduced as evidence of intent to

²⁵ First Amendment Memorandum, at 3.

²⁶ See, e.g., *id.* at 10 (speech about unapproved uses “may lead to the diversion of limited health care resources . . . on unsafe or ineffective products”); *id.* at 11 (expressing concern that, for unapproved uses, “health care providers and consumers do not have the benefit of any FDA-required labeling”); *id.* at 12 (complaining that “marketing of drugs towards health care providers drives prescribing practices, including prescribing for unapproved uses”); *id.* at 11-12 (arguing that “health care providers overestimate their knowledge” about unapproved uses).

²⁷ 564 U.S. at 567 (internal quotation marks omitted).

²⁸ *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 226 (S.D.N.Y. 2015).

²⁹ See First Amendment Memorandum at 24.

³⁰ *Amarin*, 119 F. Supp. 2d at 228.

³¹ *Id.* at 227-28. Contrary to FDA’s undeveloped assertion. see First Amendment Memorandum at 22, dicta in *United States ex rel. Polansky v. Pfizer, Inc.*, 822 F.3d 613 (2d Cir. 2016) does not revive the failed argument that FDA may use speech about an unapproved use as “evidence of intent” in a criminal or civil enforcement action alleging misbranding. *Polansky* affirmed the dismissal of a relator’s False Claims Act claims against a pharmaceutical manufacturer on the ground that an FDA-approved drug’s labeling did not purport to require compliance with certain national treatment guidelines. *Id.* at 618. In a footnote, discussing an issue not material to that outcome, the Second Circuit recognized that the government may not, consistent with the First Amendment, restrict “‘the simple promotion of a drug’s off-label use’ . . . where the promotional speech is not false or misleading.” *Id.* at 615 n.2 (quoting *Caronia*, 703 F.3d at 160). That is precisely what FDA’s regulations do in restricting manufacturer communications about unapproved uses.

³² 508 U.S. 476 (1993).

³³ 353 F.3d 947 (D.C. Cir. 2004).

support a separate illegal act. With respect to communications about unapproved uses of medical products, there is no illegal act other than speech.

If a communication about an unapproved use is truthful and non-misleading, there is little if any conceivable justification for FDA to prohibit manufacturers from conveying such information to healthcare professionals. It is difficult to envision how such a restriction on truthful, non-misleading speech could satisfy First Amendment scrutiny, particularly in light of *Sorrell*. Under any First Amendment analysis, moreover, it is especially difficult to conceive of any legitimate justification for FDA to restrict truthful, non-misleading speech when the unapproved use at issue is *medically accepted*. FDA's ability to restrict companies' speech thus is at its lowest ebb in the context of medically accepted unapproved uses. The lynchpin of regulation in this area, therefore, must be that manufacturers' truthful and non-misleading communications with healthcare professionals are presumptively protected and permissible.

C. The First Amendment Favors Disclosures Over Speech Restrictions

Rather than curtailing truthful and non-misleading communications, FDA should promote disclosure of adequate contextual information. To the extent the government has concerns about a person's protected speech, "the remedy to be applied is more speech, not enforced silence."³⁴ The First Amendment accordingly favors disclosures over restrictions on speech. It would therefore be sufficient for FDA to require that manufacturers prominently disclose contextual information, such as any scientific or statistical limitations on the data supporting the communication and other contrary studies or information.

In other contexts, FDA relies on disclosures to ensure that the recipient has all of the information necessary to make an informed assessment about the quality of the data presented. For instance, FDA's recent draft guidance regarding manufacturer communications with payors employs disclosures rather than speech restrictions: "To enable payors to make informed coverage and reimbursement decisions and to help ensure that the information is not false or misleading . . . , firms should include appropriate background and contextual information necessary to allow payors to fully understand the HCEI"³⁵ Likewise, FDA's draft guidance on communications that are consistent with FDA-approved labeling similarly proposes disclosures of context and limits on data, rather than censorship, as a means to regulate those communications. PhRMA believes that a similar system of disclosures would adequately

³⁴ *United States v. Alvarez*, 132 S. Ct. 2537, 2550 (2012) (quoting *Whitney v. California*, 274 U.S. 357, 377 (1927) (Brandeis, J., concurring); see also *Sorrell*, 131 S. Ct. at 2671 ("Vermont may be displeased that detailers who use prescriber-identifying information are effective in promoting brand-name drugs. The State can express that view through its own speech.")).

³⁵ See FDA, Draft Guidance, Drug and Device Manufacturer Communication with Payors, Formulary Committees, and Similar Entities—Questions and Answers 9 (Jan. 2017); see also *id.* at 9-14 (listing proposed disclosures).

balance the competing interests with respect to communications about medically accepted unapproved uses as well.³⁶

The First Amendment Memorandum’s criticism of disclosures as an alternative is makeweight. While acknowledging that “[w]arnings and disclosures can help provide material information necessary to assist in understanding data and their value,” the Agency cites “studies” that purportedly establish “limitations to disclosures in terms of the recipients’ perception and understanding.”³⁷ Notably, the lead study cited by FDA involved an analysis of the impact of disclosures concerning dietary supplements (i.e., not FDA-approved drugs) on consumers (i.e., not sophisticated, trained healthcare professionals).³⁸ FDA cannot plausibly extrapolate from that meta-analysis that sophisticated, trained healthcare professionals lack the ability or willingness to review and assess robust disclosures concerning FDA-approved drugs.³⁹

* * *

The foundational First Amendment principles set forth above must guide any FDA regulation of biopharmaceutical manufacturers’ communications with healthcare professionals about unapproved uses, as well as FDA’s own enforcement priorities in this area. To this end, we respond below to FDA’s specific inquiries in the hearing notice, with the goal of achieving a proper balance between maintaining FDA’s important public health mission and safeguarding biopharmaceutical companies’ First Amendment rights.

II. The PhRMA-BIO Principles Establish the Required Balance Between Protected Speech Rights and FDA’s Interests

The PhRMA-BIO Principles strike the balance required by the First Amendment between FDA’s interests and the needs of healthcare professionals to have access to information about certain available treatment options. PhRMA and FDA share interests in ensuring that communications about unapproved uses of approved medicines are truthful and non-misleading and based on sound science. Consequently, PhRMA believes the PhRMA-BIO Principles should provide the framework for FDA’s regulatory approach to manufacturer communications with healthcare professionals and payors about unapproved uses.

³⁶ See FDA, Draft Guidance, Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers Q.4./A.4., Q.6./A.6., Q.8./A.8. (Jan. 2017).

³⁷ First Amendment Memorandum, 29 & n.92.

³⁸ See Aaron S. Kesselheim et al., *Mandatory Disclaimers on Dietary Supplements Do Not Reliably Communicate the Intended Uses*, 34 HEALTH AFF. 438 (2015) (cited at First Amendment Memorandum, 29 & n.92). We discuss further flaws with FDA’s reliance on this analysis in Section IV.

³⁹ See FDA, Draft Guidance, Drug and Device Manufacturer Communication with Payors, Formulary Committees, and Similar Entities—Questions and Answers Q. A.5./A. A.5. and Q. A.7./A. A.7. (Jan. 2017) (acknowledging the sufficiency of disclosures when communicating healthcare economic information with payors, formulary committees, and similar entities).

Through several key components, the PhRMA-BIO Principles establish a framework within which manufacturers could proactively communicate truthful and non-misleading information about certain unapproved uses of their products while ensuring that patient safety and the FDA gatekeeper function remain paramount. At a minimum, we believe that FDA should permit communications (subject to the safeguards noted below) about unapproved uses of medical products that are medically accepted. These uses of drugs are supported by sufficient scientific evidence as to permit broad acceptance in the medical community for the use, even though the use itself is not FDA-approved. For such communications, the PhRMA-BIO Principles would require several safeguards, which we urge FDA to adopt.

First, PhRMA believes that all permitted communications should be based on data derived from analyses using scientifically- and statistically-sound methodologies. This safeguard helps to ensure that communications are truthful and non-misleading. Scientifically- and statistically-sound methodologies are those that are developed consistent with FDA guidelines, clinical trial protocols, and recommendations developed and endorsed by leading professional societies and thought leaders in clinical and health services research. Scrutiny of methods, protocols, or data through peer review can also help to ensure the quality of scientific methods and the integrity of the underlying data generated. FDA, of course, has long established various criteria to determine the validity and robustness of a traditional clinical trial.⁴⁰ However, PhRMA believes that additional standards derived from other sources can be applied to ensure that data are statistically- and scientifically-sound. These include: (1) data from at least one randomized, controlled clinical trial; (2) post-hoc analyses, including sub-population data; (3) observational data and real-world evidence; and (4) pharmacoeconomic information. Data from scientifically rigorous and FDA-regulated clinical studies, including Phase I-IV clinical trials that evaluate pre-specified endpoints under a clearly defined analysis plan, produce some of the most scientifically- and statistically-sound data. Post-hoc analyses, which collect safety and effectiveness information in sub-populations, can help healthcare professionals develop treatment strategies based on specific safety and efficacy data for a particular sub-population. Observational data, comparative effectiveness research, analysis of patient registries, and other real-world evidence can provide detailed and up-to-date information to help healthcare professionals understand how medical products may perform in different patient populations. Pharmacoeconomic information, including analyses of outcomes from patient population data sets, can improve the efficiency of patient care by demonstrating the value of different medicines.

Further, while PhRMA and FDA both recognize that information supported by randomized, controlled clinical trials often reflects the highest level of evidentiary substantiation, other information about medicines can meet the scientifically- and statistically-sound standard we propose. As set forth in the PhRMA-BIO Principles, post-hoc analyses, including sub-population data, observational and real-world evidence, and pharmacoeconomic information can also qualify as scientifically- and statistically-sound information. By contrast, anecdotal

⁴⁰ See, e.g., 21 C.F.R. § 314.126 (describing the characteristics of an adequate and well-controlled clinical investigation).

information or information collected through uncontrolled or biased sources would not meet this standard and would therefore be inappropriate bases for communications under a Principles-based regulatory approach. Likewise, studies based on an insufficient number of test subjects would similarly fail under this standard. The FDA's draft payer communication guidance for HCEI is an example of how such a framework could be developed for other types of communications that do not qualify as HCEI.

Second, PhRMA believes that sufficient contextual information should be included to ensure that: (a) healthcare professionals are able to weigh the validity, utility, and limitations of the information being communicated; and (b) the recipient of the information will not draw an inaccurate conclusion about the nature and quality of the evidence supporting the communication. In practice, compliance with this safeguard would entail including robust disclosures about material limitations of the information communicated. Under PhRMA's proposed approach, the substance of disclosures required will vary based on the nature of the claim being made, the complexity of information being described, the sophistication level of the intended audience, and the range of information available to the author of the relevant communication at the time it is being made. PhRMA believes that the disclosure standard should be sufficiently flexible to permit variability, as necessary, consistent with the fact that the audiences will be highly sophisticated and well-trained. But such disclosures could generally include: the regulatory status of the medicine (e.g., FDA-approved for another use, not FDA-approved); the underlying scientific research supporting such unapproved use; any limitations on the study methodologies and resulting data; manufacturer involvement in, or financial support for, the research being communicated or the organization conducting the research; and any other relevant evidence that is necessary to an informed scientific and medical judgment, including peer-reviewed contrary evidence.

Third, PhRMA believes that communications about unapproved uses should be tailored to the sophistication level of the audience receiving the communications at issue. As FDA has itself recognized in the January 2017 draft guidance documents, sophisticated audiences are more likely to comprehend limitations on data and to put communications in context (including the limitations and context provided by the proposed disclosures). Ensuring that communications are made only to healthcare professionals (physicians, payors, population health decision-makers and other sophisticated audiences) is an important safeguard to ensure the recipient of a communication has the training and expertise to fully understand the benefits and limitations of the information conveyed, including the relevance and significance of the aforementioned disclosures, and to make prescribing or purchasing decisions that are in the best interest of patient health. This is consistent with FDA's guidance that "the target audience of a promotional piece [is] critical in determining what risk information is material[;] . . . different information can be material to different audiences."⁴¹ When a manufacturer tailors a communication to the sophistication of the audience, it provides an additional assurance to FDA that the audience will be able to understand and fairly evaluate the information presented, including any limitations, and will not be misled.

⁴¹ FDA, Draft Guidance for Industry: Presenting Risk Information in Prescription Drug and Medical Device Promotion (May, 2009).

Apart from these key safeguards, under the Principles-based approach, it is important to note that PhRMA does not consider all unapproved uses as equivalent to one another. PhRMA strongly believes that communications to healthcare professionals about medically accepted unapproved uses that meet each of the standards and safeguards we have described above will be truthful and non-misleading and will protect patient health. In its First Amendment Memorandum, FDA seems to assume that all unapproved uses are equivalent in terms of their scientific substantiation, medical acceptance, and safety and efficacy profiles. Contrary to FDA's view, however, there are many examples of medically accepted unapproved uses of medicines, where patient benefits from such uses are clearly recognized. For example, both the Micromedex DRUGDEX Compendium and the NCCN Compendium list a large number of branded drugs that are associated with unapproved uses.⁴² Communications with healthcare professionals and payors about those types of unapproved uses would be permissible under PhRMA's proposed framework, so long as the communications comport with the above requirements. The caveat that such communications must meet each of PhRMA's safeguards to be permissible highlights the way in which this framework will both protect FDA's interests and also accommodate the interests of other stakeholders, such as healthcare professionals, patients, and drug manufacturers.

III. The PhRMA-BIO Principles and Proposed Safeguards Appropriately Balance All the Interests at Stake and Adequately Protect FDA's Legitimate Interests

This section describes in greater detail how PhRMA's proposed framework adequately serves FDA's public health interests and gatekeeper role in a constitutional manner, balancing the interests of patients, providers, and payors in truthful and non-misleading information sharing between manufacturers, healthcare professionals, and payors. Importantly, this section will demonstrate that all stakeholder interests can be met through the implementation of PhRMA's proposed Principles-based framework.

A. PhRMA's Proposed Communication Framework Advances FDA's Asserted Interest in Supporting Informed Decision-Making for Patient Treatment

PhRMA believes that broader manufacturer communications with healthcare professionals and payors regarding medically accepted unapproved uses will advance—not undercut—FDA's stated interest in informed decision-making for patient treatment. Because

⁴² See *infra* App. B. PhRMA analysis of branded medicines (n=46) included in the National Comprehensive Cancer Network Drugs and Biologics Compendium or the Micromedex DRUGDEX.. (See Appendix B for methodology) [*hereinafter* PhRMA Analysis of Compendia]. The analyzed drugs with listed medically accepted unapproved uses in the Micromedex DRUGDEX Compendium include Abraxane, Afinitor, Alimta, Avastin, Bendeka, Erbitux, Herceptin, Iressa, Kyprolis, Opdivo, Prolia, Xgeva, Revlimid, Tarceva, Treanda, and Velcade. The drugs with listed medically accepted unapproved uses in the NCCN Drugs and Biologics Compendium include Abraxane, Afinitor, Alimta, Alecensa, Arzerra, Avastin, Bendeka, Cabometyx, Cotellic, Cyramza, Darzalex, Emlipiti, Eritux, Farydak, Faslodex, Gazyva, Gleevec, Halaven, Herceptin, Ibrance, Imrivic, Imlygic, Iressa, Keytruda, Kyprolis, Lonsurf, Mekinist, Ninlaro, Odomzo, Onivyde, Opdivo, Prolia, Xgeva, Revlimid, Tafinlar, Tagrisso, Tarceva, Treanda, Velcade, Xtandi, Yervoy, Yondelis, Xalkori, and Zytiga.

healthcare professionals are lawfully permitted to and already prescribe FDA-approved medicines to their patients for unapproved indications, manufacturers should be permitted to share truthful and non-misleading information at a minimum about medically accepted unapproved uses of their medicines with those healthcare professionals.

As mentioned above, healthcare professionals already often prescribe FDA-approved medicines for medically accepted unapproved uses. In fact, for some diseases (for example, many rare diseases), unapproved uses represent the only available treatment option. For example, 69% of oncologists surveyed prescribe treatments for unapproved uses.⁴³

As illustrated in Table 1 below, the Micromedex DRUGDEX Compendium and the NCCN Compendium, two CMS-recognized compendia used for Medicare or Medicaid payment purposes, contain recommendations for many unapproved uses.⁴⁴ An analysis performed by PhRMA showed that 31 out of 46 medications (67%) included in the NCCN Compendium, contained a recommendation for an unapproved use. In the Micromedex DRUGDEX Compendium, 15 out of the 46 medications (33%) included a recommendation for an unapproved use.

Similarly, an analysis of the American College of Rheumatology Rheumatoid Arthritis Guidelines found that 62% (8 of 13) rheumatoid arthritis medicines analyzed included recommendations for unapproved uses. In the Infectious Diseases Society of America's clinical practice guidelines on Hospital Acquired Pneumonia and Ventilator Associated Pneumonia, 47% (7 of 15) of medications analyzed are recommended for indications outside the FDA-approved labeling.⁴⁵

Manufacturers are well-positioned to disseminate up-to-date and comprehensive information about such medically accepted unapproved uses to healthcare providers, as manufacturers possess both access to information and resources to disseminate information to providers about unapproved uses.⁴⁶ As FDA itself has long acknowledged, “[s]cientific departments within regulated companies generally maintain a large body of information on their products,” including information about off-label uses.⁴⁷ FDA also has recognized that

⁴³ See *infra* App. C. 2016 Ipsos Healthcare survey of board-certified oncologists (n=202) in practice for 2-30 years with five or more cancer patients per month. [*hereinafter* 2016 Ipsos Healthcare] (See Appendix C).

⁴⁴ NCCN Drugs & Biologics Compendium (NCCN Compendium®) https://www.nccn.org/professionals/drug_compendium/content/contents.asp; Micromedex® DRUGDEX® <https://micromedex.com/compendia>.

⁴⁵ See *infra* App. D. PhRMA analysis of American College of Rheumatology Rheumatoid Arthritis (ACR RA) Guidelines and the Infections Disease Society of America (IDSA) Clinical Practice Guidelines on Hospital Acquired Pneumonia (HAP) and Ventilator Associated Pneumonia (VAP). (See Appendix D).

⁴⁶ Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994); *United States v. Caputo*, 517 F.3d 935, 939 (7th Cir. 2008).

⁴⁷ Citizen Petition Regarding the Food and Drug Administration's Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,823 (Nov. 18, 1994).

“[e]ffective communication supports . . . optimal use of medical products . . . to maximize health.”⁴⁸ For the benefit of patients, it is imperative that FDA allow drug manufacturers to inform healthcare professionals about the medically accepted unapproved uses of their FDA-approved drugs so that they can make informed and well-reasoned treatment decisions.⁴⁹

Table 1. Examination of medically accepted unapproved uses for 46 branded medicines from CMS-recognized compendia used for Medicare or Medicaid payment purposes.⁵⁰

	NCCN Compendium	DRUGDEX Compendium
Medicines with Any Recommendation for Unapproved Use	31 (67%)	15 (33%)
Types of Unapproved Use*		
Additional Combinations Not Included on the Label	27 (59%)	7 (15%)
Subpopulations not Included in the Main Indication	8 (17%)	0
Use in Alternative Disease Progression (e.g. <i>Lines of Therapy</i>)	29 (63%)	1 (2%)
Recommendations on Other Aspects Considered for Diagnosis (e.g., <i>pregnancy, diagnostic test results, or genetic test results</i>)	13 (28%)	0

*Medicines, on average, had 1.71 (NCCN) and 1.53 (DRUGDEX) recommendations for an unapproved indication. As a result, the numbers for “Types of Investigational Uses” do not sum to the number displayed in the first row.

Healthcare professionals responsible for patient treatment decisions want access to up-to-date, truthful, and non-misleading information about medically accepted unapproved uses for the particular patients and patient populations for which they are responsible. Two surveys commissioned by PhRMA found that 78% of oncologists and 89% of specialist physicians and payors surveyed responded that it would be helpful to have more information about the safety and efficacy of unapproved uses.⁵¹ For example, more than half of the oncologists surveyed

⁴⁸ FDA, FDA’s Strategic Plan for Risk Communication (Fall, 2009), <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm183673.htm>.

⁴⁹ See James O’Reilly and Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 *Annals of Health L.* 295, 303-04 (2003); see also *United States v. Caputo*, 517 F.3d 935, 939 (7th Cir. 2008) (“[D]oesn’t it make a good deal of sense to allow speech by the device’s manufacturer, which after all will have the best information?”).

⁵⁰ PhRMA Analysis of Compendia.

⁵¹ See 2016 Ipsos Healthcare, *infra App. E*; 2016 Health Strategies Group survey of payors (managed care organization, pharmacy benefit manager, and integrated delivery network executives (n=38) and physicians

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(52%) have contacted a pharmaceutical manufacturer's medical science liaison to discuss an unapproved use. Of the oncologists who contacted a medical science liaison, 89% found the information they received useful.⁵² These results show that there is significant demand from all sectors of the healthcare system for information about uses of products outside the FDA-approved labeling. However, the current system of unsolicited requests creates significant delays in providing that information. Moreover, the system generally permits a response only to the requesting physician—most physicians who do not ask the question do not receive the information, even though the physician's patients might benefit from that information. While the FDA's new "Consistent with Label" draft guidance may help to mitigate some of these concerns with regard to data outside of the labeling but consistent with the FDA-approved indication, it does not solve these challenges with respect to unapproved uses, in particular those that are medically accepted.

The availability of accurate, balanced, and understandable information can help healthcare professionals make the best decisions for their patients.⁵³ FDA correctly noted in its Final Rule on physician labeling, for example, that "[m]ore effective communication of drug information will better inform practitioners about the risks and benefits of drugs prescribed to patients."⁵⁴ And, if healthcare professionals with access to comprehensive and accurate information make better healthcare decisions, then broader dissemination of that information would also help healthcare professionals make better treatment decisions.⁵⁵ In testimony to Congress, former Deputy Commissioner of FDA Michael Friedman opined that it is "important to good medical practice, however, that physicians have access to accurate information about drugs and how to use them."⁵⁶ Other research reinforces former Deputy Commissioner

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specialists (cardiologists, endocrinologists, hematologists, oncologists, neurologists, psychiatrists, and rheumatologists) (n=178)) [*hereinafter* 2016 Health Strategies Group survey].

⁵² See 2016 Health Strategies Group survey.

⁵³ See Stuart L. Nightingale, M.D., *Unlabeled Uses of Approved Drugs*, 26 *Drug Information J.* 141, 145 (1992) ("The principle for the FDA is that the very latest information that can be of value to physicians, pharmacists, and patients must be made available as soon as possible. Frequently, unlabeled use information is extremely important."); James M. Spears, Jeffrey K. Francer, & Natalie A. Turner, *Embracing 21st Century Information Sharing: Defining a New Paradigm for the Food and Drug Administration's Regulation of Biopharmaceutical Company Communications with Healthcare Professionals*, 70 *Food & Drug L. J.* 143, 144 (2015) ("Because almost all prescription medicines have side effects and contraindications, including some serious and fatal side effects, it is essential that healthcare professionals have access to timely, accurate, and comprehensive information about the medicines they prescribe.").

⁵⁴ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 *Fed. Reg.* at 3922, 3974 (Jan. 24, 2006).

⁵⁵ See Complaint, at 14, *Pacira Pharm., Inc. v. FDA*, No. 1:15-cv-07055 (S.D.N.Y. 2015) ("Because off-label uses are so common, information about those off-label uses, especially information concerning dosing, administration, effectiveness, and safety, is critically important to health care providers. Without access to this information, their patients may be deprived of significant health benefits and may even incur harm.").

⁵⁶ Supplemental Indications for Approved Prescription Drugs, Hearing Before the H. Comm. on Government Reform and Oversight, Subcomm. on Human Resources and Intergovernmental Relations, 104th Cong. (1996)

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Friedman's view that "too few physicians have ready access to all the data that would be useful to them as they care for patients."⁵⁷ Manufacturers should be among those permitted to provide healthcare professionals with information about medically accepted unapproved uses that can be used to make the best treatment decision for each patient. Indeed, this result is mandated by the First Amendment.

B. More Robust Manufacturer Communications Will Support FDA's Asserted Interest in Furthering Scientific Understanding and Research

Manufacturer communications with healthcare professionals also would advance FDA's stated public and individual health interests by encouraging, rather than discouraging, new scientific research.

The incentives to conduct research and to develop high-quality data that can be used to help patients rapidly diminish when a manufacturer conducting that research cannot communicate the findings. For example, James Czaban, Partner and Chair of the FDA practice group at DLA Piper LLP, emphasized at the FDA hearing the importance of being able to communicate information in the field of precision medicine, where cutting-edge research drives patient care. In his testimony, Mr. Czaban explained that: "[w]ithout the ability of innovators in this space . . . to speak about and receive information about precision medicine, the entire precision medicine initiative that the President announced will fail to meet its goals and precision medicine itself will fail to meet its potential."⁵⁸ This point is particularly relevant in a healthcare system where the availability of real world data is exploding through expanded claims databases, electronic health records, registries of patients with specific diseases, and other sources.

Additionally, FDA and Congress have both recognized the potential value of real world evidence. In the recently-enacted 21st Century Cures Act, Congress directed FDA to establish a program to evaluate the potential use of real world evidence.⁵⁹ In the new performance goals it announced under the Prescription Drug User Fee Act for Fiscal Years 2018 to 2022, FDA specifically calls out the potentially valuable role that real world evidence may play in light of "the current data revolution." As FDA stated, "it is important that FDA consider the possibilities of using so-called 'real world' data as an important tool in evaluating not only the safety of medications but also their effectiveness."⁶⁰ FDA has thus identified as a priority undertaking

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(statement of Michael Friedman, Deputy Commissioner for Operations, Food and Drug Administration, U.S. Department of Health and Human Services).

⁵⁷ Mark R. Chassin et al., *The Urgent Need to Improve Health Care Quality*, 280 J. Am. Med. Ass'n 1000, 1003 (1998).

⁵⁸ FDA hearing (Nov. 9, 2016), recording at 1:25:00.

⁵⁹ Pub. L. No. 114-255, sec. 3022 (codified at Section 505E of the Federal Food, Drug, and Cosmetic Act).

⁶⁰ See FDA, Center for Devices and Radiological Health and Center for Biologics Evaluation and Research Draft Guidance for Industry, *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*, (Updated Sept. 16, 2016) (explaining that, beyond clinical trials, "FDA recognizes that a wealth of data covering medical device experience exists and is routinely collected in the course of treatment and management of patients").

additional efforts to evaluate methodological approaches for the collection, analysis, and communication of real world evidence, among other things. Where manufacturers possess scientifically- and statistically-sound real world evidence, they should be permitted to communicate it to healthcare professionals. Permitting manufacturers to communicate information about real world evidence will incentivize manufacturers to continue developing such research, thereby furthering scientific research and understanding of the uses being studied.

C. More Robust Communications Will Further FDA's Asserted Interests in Motivating the Development of Robust Scientific Data and Ensuring Labeling is Accurate and Informative

PhRMA agrees with FDA that motivating the development of robust scientific data on safety and effectiveness and ensuring required labeling is accurate and informative are important goals, but we also believe that our proposed framework directly advances those goals. We discuss these issues below in response to the first and third public health interests related to manufacturer communications described in the First Amendment Memorandum.

PhRMA strongly believes that our proposed framework also preserves FDA's role in ensuring that product labeling provides accurate and informative information necessary for the safe and effective use of a medical product. FDA will continue to review proposed labeling under the current processes, which will preserve FDA's current oversight role.⁶¹ Additionally, PhRMA's proposed framework, including the proposed safeguards, would preserve the incentives for manufacturers to seek FDA approval/clearance and supplemental approvals, for several reasons.

First, the primary and most desirable source of information shared by manufacturers will continue to be the information contained in FDA-approved labeling. The imprimatur of FDA approval will continue to have primacy of place with healthcare decision-makers. Communication of information in the FDA-approved labeling will remain as the primary benchmark for healthcare professionals, payors, and patients. And, while unapproved uses of therapies may provide important patient benefits and may even be a standard of care, we strongly believe that the trust and credibility that FDA approval brings will continue even under a new regulatory framework, and will create a powerful incentive for manufacturers to continue to seek FDA approval for different uses of their medicines.

Second, FDA approval makes it more likely that payors, including Medicare and Medicaid, will cover and reimburse the product or use at issue. For example, payors often require prior authorization, step therapy, or other utilization management controls before a

⁶¹ For example, manufacturers will continue to submit proposed labeling as part of the New Drug Application submission process in accordance with 21 C.F.R. § 314.50 and manufacturers will continue to submit post-approval advertisements and promotional labeling with Form FDA 2253 to the Office of Prescription Drug Promotion in accordance with 21 C.F.R. § 314.81(b)(2)(iii) and (b)(3)(i). Similarly, manufacturers will still be able to voluntarily submit promotional materials to FDA for advisory comment prior to dissemination or publication in accordance with 21 C.F.R. § 202.1(j)(4).

patient will receive coverage for an unapproved use.⁶² Research has demonstrated that physicians, clinical pharmacists, and formulary committee members consider such coverage decisions and restrictions as highly influential on prescribing.⁶³ Among 38 payor organizations recently surveyed by PhRMA, 79% would still want to see the manufacturer take steps to have the use approved as an indication in the FDA-approved product labeling even if companies were able proactively to communicate more information regarding unapproved uses of a product.⁶⁴ To avoid these coverage and prescribing restrictions, manufacturers will likely continue to seek FDA approval of new products and new uses.

Third, the robust disclosures suggested for communications of information outside the FDA-approved labeling will foster a continued incentive to seek new and supplemental approvals from FDA. Manufacturers are engaging in a highly competitive environment. Having to disclose, for example, that the information they are discussing is not FDA-approved or has methodological limitations may severely dilute the message the manufacturer would like to convey. Moreover, rather than being able to present a communication in a concise and directed manner, the manufacturer would need to convey sufficient context and disclosures in connection with the substantive message. In many cases, therefore, FDA approval would allow for a more coherent (and likely stronger) message because the approval would eliminate the need to disclose certain contextual information.

Fourth, manufacturers need FDA approval in order to advertise an indication or use directly to consumers. Under current law, manufacturers are not permitted to advertise unapproved uses directly to consumers, and PhRMA is not advocating for such a change. Therefore, manufacturers will likely continue seeking FDA approvals to ensure market competitiveness through direct-to-consumer advertising. Likewise, as FDA notes and as discussed further in section III.G below, manufacturers do not enjoy marketing exclusivity for unapproved uses. The business advantages that flow from regulatory exclusivity will continue to provide strong incentives for manufacturers to seek supplemental approvals from FDA.

D. PhRMA's Proposed Safeguards Further FDA's Asserted Interests in Protecting Against Fraud, Misrepresentation, and Bias and in Protecting the Integrity and Reliability of Promotional Information

PhRMA agrees with FDA that preventing fraud and misrepresentation is an important interest. However, we again maintain that our proposed framework and associated safeguards protect this interest. We discuss these issues below in response to the second and fourth public health interests related to manufacturer communications described in the First Amendment Memorandum.

⁶² Academy of Managed Care Pharmacy, *The Academy of Managed Care Pharmacy's Concepts in Managed Care Pharmacy: Prior Authorization*, http://www.amcp.org/prior_authorization/.

⁶³ Glen Thomas Schumock et al., *Factors that influence prescribing decisions*. 38 ANNALS OF PHARMACOTHERAPY 557-562 (May 2004), available at <https://www.ncbi.nlm.nih.gov/pubmed/14966259>.

⁶⁴ See 2016 Health Strategies Group

FDA supports its concern by noting that the requirement for premarket review reflects “Congress’ determination that, where there is an absence of scientifically robust evidence, firms should not be free to market a product based merely on conjecture or rosy predictions.”⁶⁵ PhRMA firmly agrees that manufacturers must ground their communications in scientifically- and statistically-sound data, which is why we focus here on communications about medically accepted unapproved uses that are derived from scientific- and statistically-sound methodologies. These protections should prevent manufacturers from communicating misleading and potentially harmful information. Similarly, PhRMA believes that requiring all manufacturer communications to healthcare professionals and payors include appropriate context and disclosures will ameliorate the chance that manufacturers would make “deceptive or unsubstantiated claims about medical products” and will help ensure that “conclusions about the product are adequately supported and unbiased.”⁶⁶

FDA argues that only its own independent review of safety and efficacy of medicines protects the public health from uses for which the benefits do not outweigh the risks. But FDA’s view in this regard is based on paternalistic notions that physicians and other sophisticated audiences are incapable of making their own judgments about information presented. Such arguments were already considered and strongly rejected in the *Sorrell* case and we, like the Supreme Court, believe that well-trained and sophisticated healthcare professionals can review context and disclosures provided with a manufacturer communication regarding a medically accepted unapproved use and draw educated conclusions from that information.

E. The Safeguards Proposed Also Further FDA’s Asserted Interest in Preventing the Public from Harm, Including from Ineffective Treatments

PhRMA’s proposed approach, with the safeguards described, similarly would protect FDA’s stated interests in preventing harm to members of the public. FDA maintains that the speech restrictions imposed prior to FDA approval of a product are necessary because, in the absence of those restrictions, the safety and efficacy risks of many products would not be known until after patients were harmed. While PhRMA certainly agrees that preventing patient harm is an essential interest, we also believe strongly that manufacturer communications regarding medically accepted unapproved uses that follow the safeguards we have proposed are a less-restrictive way to address the risks raised by the FDA.

Healthcare professionals often prescribe medically accepted unapproved uses only when there are no approved options, or when the healthcare professional believes that use of a medicine for the medically accepted unapproved use is the best treatment option for the patient. Additionally, healthcare professionals may rely on compendia listings for unapproved uses that have not yet passed through Phase III testing but have already become medically accepted. For example, one review article in the *Journal of Clinical Pharmacy and Therapeutics* found that palliative and metastatic cancer patients who have exhausted standard lines of treatment are the

⁶⁵ First Amendment Memorandum, at 7.

⁶⁶ First Amendment Memorandum, at 7-8.

patient population most likely to be prescribed an unapproved use.⁶⁷ The same article also found that the primary reasons for the use of unapproved medicines were “(i) unapproved drug for specific tumor group; (ii) unapproved drug for specific stage of disease (neoadjuvant, adjuvant, palliative and curative); (iii) unapproved line of treatment; [and] (iv) modified application of drug (e.g. dose, frequency, combination, route of administration).”⁶⁸ Consequently, the communication framework we propose would not only preclude false or misleading communications—thus ameliorating the concerns FDA raises—but our approach also would foster better patient outcomes by informing physicians of the safety and effectiveness of unapproved uses when there is medical acceptance of such uses, through communications based on scientifically- and statistically-sound underpinnings. This is particularly true where approved alternatives raise greater safety risks or are demonstrably ineffective. Our framework is thus better tailored than the FDA proposal, which allows for no exceptions.

The First Amendment Memorandum does not support the broad restrictions of speech sought by FDA. In support of its proposed restrictions on manufacturer communications, FDA cites “the results of the Canadian study showing an association between unapproved uses and adverse drug events” which was released in January 2016.⁶⁹ In the Study Abstract, the authors note that “[t]he rate of [Adverse Drug Events (‘ADE’)] for off-label use (19.7 per 10,000 person-months) was higher than that for on-label use (12.5 per 10,000 person-months)” and that “[o]ff-label use lacking strong scientific evidence had a higher ADE rate (21.7 per 10,000 person-months) compared with on-label use.”⁷⁰ “However, off-label use with strong scientific evidence had the same risk for ADEs as on-label use.”⁷¹ According to the authors, “strong evidence” existed when “(1) the drug is effective or favors efficacy for the off-label treatment indication, (2) is recommended for at least most patients with the off-label treatment indication, and (3) the studies used to evaluate efficacy and the strength of evidence include at least 1 randomized controlled trial.”⁷²

While the authors of the Canadian study properly note the value of scientifically sound information, they improperly dismiss many types of important evidence that can be valuable to healthcare professionals even though it is not supported by randomized controlled trials. As the authors of the Canadian study acknowledge, “[o]ff-label use may be clinically appropriate given the complexities of the patient’s condition, the lack of alternative effective drugs, or after exhausting approved drugs. However . . . [p]hysicians are finding it difficult to keep up with rapidly changing medication information, and this lack of knowledge is affecting treatment of

⁶⁷ Mohd Masnoon Saiyed et al., *Off-label drug use in oncology: a systematic review of literature*, J. OF CLINICAL PHARMACY AND THERAPEUTICS 1 (2017).

⁶⁸ *Id.* at 2.

⁶⁹ First Amendment Memorandum at 23-24.

⁷⁰ Tewodros Eguale, et. al., Association of Off-Label Drug Use and Adverse Drug Events in an Adult Population, 176 JAMA INTERN MED 55 (2015).

⁷¹ *Id.* (emphasis added).

⁷² *Id.* at 57.

patients.”⁷³ PhRMA’s approach permits communications about unapproved uses where there is a scientifically and statistically sound methodology supporting it and where the use is medically accepted. It thus balances the competing interests in a manner that takes into account the important patient health considerations acknowledged in the Canadian study. We encourage the FDA to adopt PhRMA’s approach.

PhRMA also strongly believes that sophisticated payors and population health decision-makers will help prevent the diversion of limited healthcare resources through their decisions not to reimburse any ineffective, unsafe, or unproven use of a drug. First Amendment principles mandate that such decision-makers be permitted to evaluate clinical communications just as they can economic communications. Similarly, to prevent harm to their patient populations, healthcare professionals would not choose to prescribe any ineffective, unsafe, or unproven use of a drug, thereby also helping to prevent the diversion of limited healthcare resources. The FDA’s paternalistic concerns that physicians and other sophisticated audiences will not understand truthful and non-misleading information conveyed to them, with appropriate disclosures, are out of step with the First Amendment case law and cannot support restrictions of truthful and non-misleading speech.

F. PhRMA’s Proposed Communication Framework Furthers FDA’s Asserted Interests in Protecting Human Research Participants, Ensuring Informed Consent, and Maintaining Incentives for Clinical Trial Participation

FDA’s attempt to support its existing restrictions on manufacturer communications based on its interests in protecting human participants receiving experimental treatments, ensuring informed consent, and maintaining incentives for clinical trial participation is misplaced. PhRMA again agrees that it is an important public health goal to protect clinical trial participants receiving experimental treatments, and also a legitimate goal to maintain incentives for clinical trial participation. However, FDA’s restrictions on manufacturer communications have at best a tangential relationship to these public health interests, and do not directly advance these interests or constitute a narrowly-tailored mechanism for meeting the interests.

FDA is explicit in its regulations governing clinical trials that use of an approved medicine for an unapproved use in the course of a healthcare professional treating a patient does not constitute an experimental clinical investigation but rather the practice of medicine.⁷⁴ FDA does not explain in its First Amendment Memorandum how restrictions on manufacturer communications foster informed consent or other protections for clinical trial participants when FDA itself does not treat the use of a medicine for an unlabeled use in the practice of medicine as the sort of experimental treatment that triggers these clinical trial requirements in the first instance. Of course, the full panoply of FDA regulatory requirements (*e.g.*, informed consent and institutional review board approval) will continue to apply to actual clinical trials, whatever modified policies FDA adopts for manufacturer communications.

⁷³ *Id.* at 60.

⁷⁴ 21 C.F.R. § 312.2(d) (FDA’s IND regulations “do[] not apply to the use in the practice of medicine for an unlabeled indication of [an approved] new drug product . . . or licensed biological product”).

Even with FDA's current restrictions on manufacturer communications, when a patient is prescribed a drug for an unlabeled indication, the heightened informed consent process and other regulations governing clinical trials do not apply. At the same time, FDA's existing restrictions on communications limit the information flowing to the prescriber and hence impede, rather than enhance, informed decision-making when drugs are used outside their labeling. FDA has thus ironically cited its interest in informed treatment as a rationale to prevent manufacturers from informing prescribers about available scientific and medical information.

FDA's restrictions on manufacturer communications also are not necessary to preserve incentives for clinical trial participation. FDA provides no references or other evidence to support its assertion that expanded manufacturer communications concerning unapproved uses of a product could undermine the clinical trial process.⁷⁵ To the contrary, allowing increased communications with healthcare professionals about new medicines and new uses of FDA-approved medicines should increase, rather than hinder, patient incentives to enroll in clinical trials. Providing reliable information to healthcare professionals about potential treatments in the research pipeline would improve provider awareness of trials important to their patients. This additional access to information will enable health care professionals to serve as intermediaries and trusted advisors for trial participants, which in turn will reduce recruitment time, increase the availability of potential participants, accelerate the commencement of trials, and potentially improve the quality of the resulting data.

To illustrate this point, in connection with preparing this comment letter, PhRMA conducted a survey of payors and physician specialists. Among 178 specialist physicians surveyed, nearly two-thirds (66%) agreed that if they had more information about unapproved uses, they would more often refer patients to clinical trials that seek to develop evidence about the benefits of these uses. Additionally, 28% of the specialists said the availability of information on unapproved uses would have no impact on their referral of patients to clinical trials, and only 6% indicated they would be less likely to refer patients to clinical trials if more information on unapproved uses was made available.⁷⁶ Similarly, among a panel of 202 board-certified oncologists surveyed, 77% reported that they would be more likely to refer patients to a clinical trial if they had more information on unapproved uses.⁷⁷

If FDA modifies its policies on manufacturer communications, manufacturers will continue to have robust incentives to generate new data through clinical trials in order to seek expanded labeling. As discussed above, among other things, FDA approval of new labeling facilitates prescriber adoption because of the high standard that FDA approval connotes. FDA approval also supports coverage and reimbursement of a new use by payors. FDA thus may not justify ongoing restrictions on manufacturer communications as necessary either to preserve clinical trial protections or to ensure adequate clinical trial participation.

⁷⁵ First Amendment Memorandum, at 14.

⁷⁶ 2016 Health Strategies Group survey.

⁷⁷ 2016 Ipsos Healthcare.

G. FDA's Stated Interests in Protecting Innovation Incentives and in Protecting Incentives for the Development of Products for Underserved Patients Do Not Support Broad Restrictions on Manufacturer Communications

FDA rightfully notes the important role that patent protection and periods of non-patent exclusivity play in creating incentives for firms to invest in research and development and bring new drugs and new drug uses to market, both in general and in the case of medicines for orphan diseases and conditions. Preservation of these incentives for innovation is critical. However, there is only a narrow set of circumstances in which these incentives for innovation are affected by FDA rules restricting manufacturer communications: the special circumstance where there is an exclusivity-protected supplemental use and an unprotected prior use and FDA then approves a subsequent abbreviated new drug application (“ANDA”), 505(b)(2) application, or, in the case of orphan exclusivity, a New Drug Application (“NDA”) or Biologics License Application (“BLA”) for the same drug. In these very limited and specific circumstances only, a prohibition on off-label communications would directly advance the government’s legitimate interest in preserving incentives for innovation and no less restrictive alternative would be viable, such as a disclaimer. Further explanation of these issues follows, first for the case of non-orphan drugs and then for orphan drugs.

1. Non-Orphan Innovation Incentives

As a starting matter, FDA’s rules for manufacturer communications do not alter applicable patent rights. If a competitor’s communications about its product for an unapproved use somehow infringe the valid patent rights of another company regarding the use at issue, then the infringed party may pursue a claim under the patent laws. FDA rules for manufacturer communications are not germane to the underlying patent rights. There is no need to maintain restrictions on manufacturer communications in order to preserve meaningful patent protection for a product or product use.

Non-patent exclusivity, except in the case of orphan drug exclusivity, only applies against ANDAs, section 505(b)(2) applications, or biosimilar applications.⁷⁸ Accordingly, the ability of the holders of innovator NDAs approved under section 505(b)(1) of the FDCA or full BLAs approved under section 351(a) of the Public Health Service Act to communicate about unapproved uses of their products has no potential impact on the non-orphan exclusivity rights of others. Even as to ANDA, 505(b)(2), and biosimilar applicants, FDA rules on manufacturer communications have no bearing on new chemical entity (“NCE”) exclusivity or biologics reference product exclusivity. Those forms of exclusivity bar either submission or approval of an ANDA,⁷⁹ 505(b)(2) application,⁸⁰ or biosimilar application.⁸¹ Neither eligibility for these

⁷⁸ 21 U.S.C. §§ 355(c)(3)(E), (j)(5)(F); 42 U.S.C. § 262(k)(7).

⁷⁹ 21 U.S.C. § 355(j)(5)(F).

⁸⁰ 21 U.S.C. § 355(c)(3)(E).

⁸¹ 42 U.S.C. § 262(k)(7).

forms of exclusivity nor their scope are affected by FDA rules for manufacturer communications about unapproved uses of approved products. For example, regardless of manufacturer communications, an ANDA or section 505(b)(2) application referencing a drug with NCE exclusivity could not be submitted for the duration of exclusivity, and therefore no generic or 505(b)(2) company communications could be put forth to undermine the NCE exclusivity incentive. Because these incentives for NCE exclusivity will not be impacted by manufacturer communications, FDA may not justify its ongoing restrictions on manufacturer communications based on its interest in preserving NCE exclusivity as an incentive for innovation. The same is true for biologics reference product exclusivity.

That leaves three-year exclusivity for a new use as the only form of non-orphan exclusivity implicated by FDA rules for manufacturer communications. For this particular category, FDA's communications policies may help protect incentives for product innovation. The reason is that in this very particular circumstance, a competitor could seek approval of a 505(b)(2) application or ANDA without labeling for the protected supplemental use at issue,⁸² but then promote its drug off-label for the protected use, subject to potential infringement claims under any applicable patents.⁸³ FDA's restriction on off-label communications in this special case directly advances the government's interest in preserving the incentive to develop new supplemental uses in the first instance, and there is no apparent less restrictive alternative other than a full prohibition on the promotion of the off-label protected supplemental use.

The constitutional analysis in these narrow circumstances is fundamentally different than where a restriction on speech is not serving to protect a new use protected by exclusivity. Rather than identifying and analyzing the Agency's specific interests in these various circumstances, FDA broadly claims in the First Amendment Memorandum that promoting drugs for unapproved uses otherwise "protected by patents or exclusivity held by another applicant" would undermine "incentives for innovation."⁸⁴ However, the Agency's interest in protecting non-orphan incentives for innovation is furthered only in the narrow circumstance of communications by an ANDA or 505(b)(2) application holder regarding a use protected by three-year exclusivity. FDA should revise its analysis to account for the various forms of exclusivity incentives available under Hatch-Waxman and the very limited circumstances under which FDA's interest in preserving three-year exclusivity incentives is directly advanced by speech restrictions.

2. Incentives for Orphan Drugs

FDA's citation to incentives and programs it maintains to encourage the development of treatments for underserved patients suffers from the same flaw as FDA's discussion of the statutory exclusivities discussed in the prior section—the incentives and programs are quite

⁸² See, e.g., 21 U.S.C. § 505(j)(5)(B)(iii).

⁸³ Despite the labeling omissions, and with no generic company promotion of its product for the unapproved (exclusivity-protected use) use, the generic drug may be substituted at the pharmacy when dispensing a prescription for the exclusivity-protected use.

⁸⁴ First Amendment Memorandum at 15, lines 406-09.

important, but they are not affected by FDA's policies on manufacturer communications except for very narrow and specific circumstances. PhRMA members are acutely aware of the need to develop medicines for underserved patients, particularly treatment options for small patient populations with rare diseases and conditions. Biopharmaceutical research companies are currently developing more than 560 medicines for rare diseases, including for rare cancers, genetic disorders, neurological disorders, infectious diseases, and autoimmune diseases.⁸⁵ Through various incentives and programs in the past three decades, FDA's Office of Orphan Products Development has enabled over 600 drug and biologic products for rare diseases to be marketed in the United States.⁸⁶ These incentives have proven incredibly effective, and PhRMA supports FDA's legitimate interest in ensuring that firms continue to invest in the development of products for underserved patients.

FDA asserts that "[i]f firms promote their approved or cleared medical products for unapproved uses, [its] incentives and programs could be weakened."⁸⁷ However, FDA provides no explanation for this statement, and the risk to these incentives only arises in specific and narrow circumstances. Most of the programs that FDA references would not be affected at all by communications about unapproved uses. For example, the Rare Pediatric Disease Priority Review Voucher Program provides a voucher that can be redeemed for subsequent priority review as an incentive to develop drugs for rare pediatric diseases.⁸⁸ This is an incentive to develop a treatment for a rare pediatric disease, and provides a benefit for review of a subsequent application. This incentive is wholly unaffected by FDA's communications policies. The same is also true of other programs aimed at incentivizing development of drugs for underserved patients, including FDA's fast track, breakthrough therapy, accelerated approval, priority review designation, Orphan Products Clinical Trials Grants Program, and Orphan Products Natural History Grants Program, as well as the tax incentives and user fee waivers that exist for orphan drug development. Modifying FDA's current restraints on manufacturing communications would have no impact on these programs, and maintaining those restrictions on speech does not directly advance FDA's interest in encouraging drug development through these programs. Orphan drug exclusivity would potentially be impacted by a change in FDA's manufacturer communication policies, but only in narrow circumstances. FDA may not justify broad speech restrictions as necessary to preserve the incentives from orphan exclusivity outside these narrow circumstances.

⁸⁵ See Press Release: More Than 560 Medicines in Development for Rare Diseases, PhRMA (2015), <http://www.phrma.org/press-release/phrma-and-the-als-association-report-more-than-560-medicines-in-development-for-rare-diseases>; see also 2016 Medicines in Development for Rare Diseases, PhRMA (2016), <http://phrma-docs.phrma.org/sites/default/files/pdf/medicines-in-development-drug-list-rare-diseases.pdf>.

⁸⁶ See Developing Products for Rare Diseases & Conditions, U.S. Food & Drug Admin., <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm> (last visited Mar. 3, 2017).

⁸⁷ First Amendment Memo at 16.

⁸⁸ See 21 U.S.C. § 360ff.

Orphan drug exclusivity applies only to applications for the same drug as the one with the exclusivity. This means that expanding the ability of manufacturers of different drugs to communicate about unapproved uses of their products generally will not undermine orphan exclusivity, because orphan exclusivity applies to a particular drug for a particular use. For example, if a company has orphan exclusivity for a drug approved for a particular type of orphan cancer, that exclusivity will not apply to another company's different drug for that same cancer, and so the other company's communications about its drug for that cancer cannot be viewed as undermining the first company's orphan exclusivity. Similarly, where a drug is approved *only* for a use protected by orphan exclusivity, no competing version of that drug may be approved under an ANDA, 505(b)(2) application, 505(b)(1) NDA, or BLA, and there is again no issue with competitor communications about an unapproved use of an approved product undermining orphan exclusivity.

That leaves the only scenario under which orphan drug exclusivity may be impacted by manufacturer communications about unapproved uses as one in which an innovator company has a drug approved for one use protected by orphan drug exclusivity and also approved for other unprotected uses. In that instance, absent an FDA prohibition on off-label promotion, a competing ANDA, 505(b)(2) application, full NDA, or BLA could be approved for the drug at issue for the unprotected uses, but then promoted off-label for the protected orphan use. In this special circumstance, the off-label promotion would undermine the orphan drug exclusivity earned by the original NDA or BLA holder. Limiting off-label promotion by the competing products for the orphan-protected indication thus could help protect incentives for pursuing the orphan use in the first instance. However, as with three-year exclusivity, this is a very narrow circumstance in which the speech restriction directly advances the government's interest and there is no apparent less-restrictive alternative. This government interest does not justify broad restrictions on manufacturer communications under First Amendment principles.

In its First Amendment Memorandum, FDA does not acknowledge the complex nature of incentives for developing orphan drugs. FDA does not address whether communications about unapproved uses would meaningfully alter these incentives, or whether or how seeking to preserve these incentives justifies a restriction of manufacturer communications. FDA does not cite any literature or other findings supporting its broad claim that these incentives "could be weakened" by a change in its promotion rules. FDA should revise its analysis to account for the distinction between its expedited approval programs—which are not affected by FDA's rules on manufacturer communications—and incentives for pursuing orphan drug designations as discussed above. FDA must account for this distinction and acknowledge that its interests in preserving incentives only justify speech restrictions in narrow circumstances.

IV. Patients, Providers, and Payors Also Have Critical Interests in Truthful Information About Beneficial Uses that Need To Be Carefully Considered in Order To Comply with the First Amendment

Before FDA can restrict protected speech between manufacturers, healthcare professionals and payors consistent with the First Amendment, FDA has the burden of fully considering viable alternatives that are less restrictive of speech, including a consideration of

whether any alternative approaches would be viable if they were subject to the safeguards in the PhRMA-BIO Principles. While we agree that many of the alternatives that FDA describes in its First Amendment Memorandum are neither reasonable nor feasible, other alternatives are viable. We thus disagree that FDA's conclusions with regard to available alternatives are sufficient to justify existing restrictions on truthful, non-misleading manufacturer speech.

For example, FDA dismisses the alternative of “[a]llowing firms to actively promote an unapproved use as long as they disclose that the use is unapproved and include other appropriate warnings.” FDA rejects this approach because “studies show there are limitations to disclosures in terms of the recipients’ perception and understanding.”⁸⁹ However, as the PhRMA-BIO Principles and our proposed safeguards illustrate, a disclosure-based alternative could be a viable alternative to the more restrictive regulatory approach FDA has adopted with regard to communications about unapproved uses. FDA has provided insufficient constitutional grounds for dismissing this alternative in favor of a more-restrictive and, we would argue, unconstitutional regulatory approach.

Notably, the studies cited by FDA to support the asserted impracticality of this first alternative do not support the proposition for which they are cited. For example, the 2015 Kesselheim article cited in footnote 92 of the First Amendment Memorandum as the lead support for the proposition that “studies show there are limitations to disclosures in terms of the recipients’ perception and understanding” does not come close to supporting that well-trained physicians would be misled by disclosures of context concerning medically accepted unapproved uses. To the contrary, the article recognizes that “some of the randomized studies were conducted using student volunteers and might not be generalizable to typical consumers of medications.” Moreover, the article studies the effect of disclaimers in the context of dietary supplements, which “might not predict the effect of disclaimers applied to other treatments, such as prescription medications.” The authors “found no studies that tested physicians’ responses to disclaimers” and “found no studies that addressed disclaimers related to prescription drugs.”⁹⁰ Research conducted in early 2017 supports the conclusion that there is a lack of peer-reviewed literature studying the impact of disclosures and disclaimers related to prescription medicines on physician response.⁹¹ Because the purpose of the Part 15 notice process is to create a regulatory framework for communications to healthcare professionals, it is particularly alarming that FDA based its rejection of an important alternative to the current framework on a study (a) involving communications to consumers—not doctors — (b) relating to dietary supplements—not prescription drugs—and (c) that explicitly disclaimed generalizability to other consumers of

⁸⁹ First Amendment Memorandum, at 29.

⁹⁰ Aaron S. Kesselheim et al., *Mandatory Disclaimers On Dietary Supplements Do Not Reliably Communicate the Intended Issues*, 34 *Health Affairs* 438, 440 (2015).

⁹¹ Xcenda literature review conducted in March 2017 using keyword searches on PubMed. Reference lists from related articles were also scanned for potential further reference citations. Several articles related to the policy of unapproved medicine use were located. However, any information mentioned about disclaimers/disclosures in these articles was not informative for establishing physician responses to disclosures or the overall effectiveness of disclaimers related to prescription medicines. *See infra* App. F.

healthcare beyond those studied. This analysis comes nowhere close to meeting the First Amendment burden of proof for censoring protected speech.

Similarly, FDA is also too quick to dismiss the option of “[p]ermit[ing] promotion of unapproved uses listed in medical compendia.” While it is no doubt true that not all unapproved uses are safe and effective, a compendium listing is an important indicator of medically accepted unapproved use. The information contained in reputable CMS-recognized compendia is reliable and accepted throughout the medical community. However, PhRMA recognizes that a communication improperly influenced by compendia listings would not be consistent with the PhRMA-BIO Principles. Therefore, FDA should not simply dismiss these sources of substantiation due to the possibility—however remote—that industry sponsorship could lead to bias in such listings and therefore result in misleading communications. For example, this supposed risk could easily be overcome by disclosing that the cited compendium was developed with support from a pharmaceutical manufacturer. That disclosure, along with other context-specific disclosures, would create an appropriate balance that protects the FDA’s interest without restricting speech.

Finally, FDA suggests that the alternative of “[l]imiting evidence that could be considered relevant to intended use to speech that the government can prove is false or misleading” is also not viable. We disagree. As with the first two alternatives, this third alternative approach could preserve the FDA’s true interests in a manner less restrictive of speech than the current approach. FDA’s concern that “firms might be free to actively promote unapproved uses . . . based on incomplete, unbalanced, or non-objective data or information” is a misplaced one.⁹² As PhRMA’s proposed approach demonstrates, safeguards focused on the quality of the underlying data, disclosure of relevant contextual limitations, and audience considerations would mitigate the FDA’s asserted concerns. FDA also argues that this approach would “open the door to statements by a ‘true believer’ who truthfully represents he believes a product cures cancer without any scientific basis for that conclusion.”⁹³ That, of course, is false. PhRMA’s alternative, as set forth in the PhRMA-BIO Principles, requires that communications must be based on data derived from analyses using scientifically- and statistically-sound methodologies and must provide appropriate context. In other words, FDA’s concern is speculative at best and does not justify censorship. PhRMA’s proposed alternative protects FDA’s interests and is less restrictive of speech. It is thus constitutionally mandated.

While PhRMA disagrees with FDA that the three alternative approaches discussed above are not viable, we do agree that the other alternative approaches described in the First Amendment Memorandum are neither reasonable nor feasible. For example, PhRMA agrees that “[p]rohibiting altogether the use and/or prescribing of an approved/cleared medical product for an unapproved new use” would infringe on the prohibition on FDA’s ability to regulate the practice of medicine, which could be potentially injurious to public health.⁹⁴ PhRMA agrees that

⁹² First Amendment Memorandum, at 33.

⁹³ *See id.* at 34.

⁹⁴ *Id.* at 26.

“[c]reating ceilings or caps on the number of prescriptions for an unapproved use” is not appropriate because this approach would adversely impact the public health, would be impractical to implement and monitor, and could infringe on the practice of medicine.⁹⁵

We agree that “requiring firms to list all potential indications for a product in the initial premarket application” would be impractical to administer and could ultimately be harmful to patients. We also agree that “[p]rohibiting specific unapproved uses that are exceptionally concerning or developing tiers based on level of safety concerns with greater regulatory controls for the relatively higher risk products” would not be a reasonable alternative, in part because allowing communications based only on the level of safety concerns would undermine incentives to conduct research to demonstrate both safety and effectiveness.⁹⁶ PhRMA further agrees that “[r]equiring firms to list all potential indications for a product in the initial premarket application” might delay approval/clearance of new products and negatively impact public health because it is impossible to know all of the potential uses of a medical product from the initial studies. PhRMA agrees with FDA that “[r]eminding healthcare providers of potential malpractice liability” would be counter to FDA’s interest in allowing healthcare professionals to determine the best treatment options for their patients.⁹⁷ We also agree that “[t]axing firms more heavily for sales of products for unapproved uses than for approved uses” would not align with FDA’s interest in allowing healthcare providers to freely prescribe medical products for their patients, and would be impractical to monitor and enforce.⁹⁸

Additionally, while we agree that “[e]ducating healthcare providers and patients to differentiate false and misleading promotion from truthful and non-misleading information” would not be sufficient to meet all of the interests at stake, we encourage FDA to review this alternative further.⁹⁹ FDA should consider the existence of FDA-sponsored outreach programs, such as the Bad Ad Program, which is designed to educate healthcare professionals about prescription drug advertising and promotion. Other FDA publicity tools and FDA’s ability to send “It Has Come to Our Attention” letters demonstrate that FDA has not sufficiently considered this alternative approach as one aspect of a regulatory framework regarding manufacturer communications to healthcare providers. We note in this regard that basic First Amendment principles support that the response to speech with which FDA disagrees is more speech, not prior restraint.

Under the PhRMA-BIO Principles, FDA of course would continue to have authority to police false or misleading promotional practices. For example, FDA could still take exception to a manufacturer’s failure to disclose limitations of underlying scientific data or safety issues specific to certain subpopulations. FDA could object to communications if there is insufficient

⁹⁵ *Id.* at 27.

⁹⁶ *Id.*

⁹⁷ *Id.* at 31.

⁹⁸ *Id.* at 32.

⁹⁹ *Id.* at 30.

disclosure of context or the communication is otherwise false or misleading. And, FDA could object to communications about unapproved uses to unsophisticated audiences, such as patients. Thus, citation to past settlements on specific fact patterns does not support unconditional restriction of First Amendment protected speech. We strongly believe that PhRMA's proposed framework is the correct approach, incorporating and building on the positive aspects of some of the alternative approaches discussed in the First Amendment Memorandum, but balancing the interests in a way that considers all elements of the government's burden of proof under the First Amendment case law.

V. Proposed Regulatory Changes

We believe FDA should implement our proposed framework for manufacturer communications to healthcare professionals described in the preceding sections of these comments. To recommend specific regulatory changes, PhRMA reviewed FDA's regulations on advertising and promotion as well as the related guidance documents. FDA's existing regulations for advertising and promotional labeling include limitations on communications that contain information outside the approved labeling for a drug or that otherwise do not meet the traditional standard of "substantial evidence." These regulations represent an overly-restrictive approach that limits truthful and non-misleading communications that are both in the interest of public health and within the full scope of First Amendment protection. Further, these regulations seem potentially to be inconsistent with certain aspects of the recent FDA draft guidance expressly permitting certain forms of communication. For these reasons, PhRMA recommends that FDA consider amending the following key areas of its regulations that historically have been applied to restrict pharmaceutical manufacturers' truthful and non-misleading speech.¹⁰⁰

A. Requirements for "Substantial Evidence" to Support Advertising and Promotional Labeling

FDA has traditionally required promotional communications regarding the safety or efficacy of a drug to be supported by "substantial evidence," generally meaning "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved."¹⁰¹ This requirement for drug advertising and promotion is derived from the statutory provisions governing drug approval, which require FDA to withhold approval of a new drug unless, among other things, the effectiveness of the drug is supported by substantial evidence.¹⁰² However, FDA has adopted the substantial evidence standard to require such adequate and well-

¹⁰⁰ The statutory sections and FDA regulations discussed in these comments apply to drugs and biologics. Biological products such as vaccines, blood products, monoclonal antibodies, and cell therapies meet the definition of a "drug" under the FDCA. FDA licenses biological products for marketing under the Public Health Service Act, rather than approving them under the FDCA. However, except for licensure and certain other statutory or regulatory provisions specifically directed at biologics, the legal provisions governing drugs generally apply to biological products as well. *See* Public Health Service Act § 351(j); 42 U.S.C. § 262(j).

¹⁰¹ *See* FDCA § 505(d)(5); 21 U.S.C. § 355(d)(5); *see also* 21 C.F.R. § 314.126.

¹⁰² *See* FDCA § 505(d)(5); 21 U.S.C. § 355(d)(5).

controlled investigations in its regulations governing prescription drug advertisements and then extended the requirement to promotional labeling.

For prescription drug advertisements, section 502(n) of the FDCA requires that all drug advertisements include “true statements” of the drug name, formula, and other information relating to side effects, contraindications, and effectiveness. In 21 C.F.R. § 202.1(e)(5)-(6), FDA construes this “true statement” provision to require substantial evidence in order for such statements to be truthful and non-misleading.¹⁰³ Similarly, for promotional labeling, in applying statutory requirements that such labeling not be false or misleading in any particular,¹⁰⁴ FDA has imposed the same requirements set forth in its regulations for advertisements. For example, FDA’s labeling regulations at 21 C.F.R. § 201.56(a)(3) and § 201.100(d) prohibit labeling from including any “implied claims or suggestions of drug use ... if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness.”¹⁰⁵ As a result, FDA under its regulations considers promotional labeling to be false or misleading and in violation of law if it contains claims not supported by substantial evidence.

FDA construes these requirements for substantial evidence to limit the ability of manufacturers to share important information that does not rise to this level of substantiation. Yet, as noted above, information based on pharmacoeconomic data, post-hoc analyses of clinical trial results, sub-population analyses, observational data, real world evidence or results from clinical experience, treatment guidelines, and other such information can provide relevant context and valuable information about drug use, even where they do not meet the standard for substantial evidence. We thus strongly encourage FDA to amend its regulations to provide that information not meeting the substantial evidence standard nevertheless may be communicated if based on scientifically- and statistically-sound methodologies and communicated in a truthful and non-misleading manner.

To do this, FDA should adopt a savings clause in 21 C.F.R. § 202.1(e)(5)-(6) to provide that statements that are based on sound scientific methodologies and truthful and non-misleading, although not based on substantial evidence, do not violate the statutory requirement

¹⁰³ Among other things, prescription drug advertisement regulations list false and misleading violations that include statements about the safety, effectiveness, or use of an approved drug that have not been demonstrated by “substantial evidence” or “substantial clinical experience.” *See, e.g.*, 21 C.F.R. § 202.1(e)(6)(i) (prohibiting any advertisement containing “a representation or suggestion, not approved or permitted for use in the labeling, that a drug is better, more effective, useful in a broader range of conditions or patients . . . , safer, has fewer, or less incidence of, or less serious side effects or contraindications than has been demonstrated by substantial evidence or substantial clinical experience”); 21 C.F.R. § 202.1(e)(6)(ii) (prohibiting drug comparisons not supported by substantial evidence or substantial clinical experience).

¹⁰⁴ *See* FDCA § 502(a); 21 U.S.C. § 352(a).

¹⁰⁵ *See* 21 C.F.R. §§ 201.56(a) (setting forth general requirements for labeling for all drugs described in § 201.100(d), including that drug use claims be based on “substantial evidence of effectiveness”), 201.100(d) (describing labeling “whether or not it is on or within a package from which the drug is to be dispensed,” distributed by or on behalf of the manufacturer, packer, or distributor,” that furnishes information for use or suggesting dosage for use of a drug).

that advertisements consist of “true statements.” Similarly, FDA should add a savings clause to its labeling regulations in 21 C.F.R. § 201.56 and § 201.100(d) to provide that these provisions do not restrict truthful, non-misleading speech regarding unapproved uses of FDA-approved products. FDA should further clarify that regulatory requirements for substantial evidence in the approved prescribing information, such as those in 21 C.F.R. § 201.57(c)(2)(iii) or § 201.80, apply only to the approved prescribing information and do not otherwise prohibit truthful non-misleading communications.¹⁰⁶ Such revisions would conform FDA regulations to the First Amendment principles discussed above, and also would reconcile the regulations with the FDA’s recent draft guidance documents, which permit communication of information based on evidentiary support that does not comport with the drug approval standard.¹⁰⁷

B. Requirements for “Adequate Direction for Use” and Exemptions for Prescription Drug Labeling

Section 502(f) of the FDCA requires drug labeling to bear “adequate direction for use” to avoid being deemed misbranded. FDA has construed this provision to require “directions under which the layman can use a drug safely and for the purposes for which it is intended.”¹⁰⁸ Because prescription drugs must be used under the supervision of a licensed health care professional, the labeling thus cannot provide adequate directions for a layperson,¹⁰⁹ and FDA has by regulation created exemptions from the statutory adequate direction for use requirement for prescription drugs. However, through these exemptions from the statutory adequate direction for use requirement, FDA has imposed overly broad limits on what information pharmaceutical manufacturers may communicate.

FDA’s exemption criteria for prescriptions drugs are set forth in Subpart D of its labeling regulations. In 21 C.F.R. § 201.100(c), FDA provides that, in order for FDA-approved prescribing information (the labeling “on or within the package from which the drug is to be dispensed”) to be exempt from the statutory adequate direction for use requirement, the labeling

¹⁰⁶ PhRMA appreciates that the FDA’s Draft “Consistent with Labeling” guidance concurs that the substantial evidence standard for approval is not applicable to communications consistent with the FDA-approved label, but PhRMA believes that the concepts in the PhRMA-BIO Principles document should also be incorporated into FDA’s regulations.

¹⁰⁷ See Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities, Draft Guidance, 82 Fed. Reg. 6568 (Jan. 19, 2017) (providing that the communication of HCEI would not be considered false or misleading if it is “based on competent and reliable scientific evidence” that “has been developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results”); Medical Product Communications That Are Consistent With the FDA-Required Labeling, Draft Guidance, 82 Fed. Reg. 6575 (Jan. 19, 2017) (providing that consistent with labeling communications “should be scientifically appropriate and statistically sound to support the representations or suggestions made in the communication,” where such information will not be considered false or misleading “based only on the lack of evidence sufficient to satisfy the applicable approval/clearance standard” (i.e., substantial evidence in the case of drugs)).

¹⁰⁸ 21 C.F.R. § 201.5.

¹⁰⁹ FDCA § 503(b)(1); 21 U.S.C. § 353(b)(1).

must provide licensed professionals “adequate information” to “use the drug safely and for the purposes for which it is intended,” where the labeling “is the labeling authorized by the approved new drug application or required as a condition for the certification or the exemption from certification requirements.”¹¹⁰ Similarly, in 21 C.F.R. § 201.100(d), FDA provides that all labeling, regardless of whether it is included on or within the drug packaging and so extending to promotional labeling in addition to the approved prescribing information, must provide licensed professionals “adequate information” to “use the drug safely and for the purposes for which it is intended,” where the adequate information must be “the same in language and emphasis as labeling approved or permitted” by FDA.¹¹¹

Through these regulations, FDA has transformed truthful and non-misleading communications outside of a product’s approved prescribing information into a misbranding violation under Section 502(f) of the FDCA. To avoid being misbranded under current regulations, labeling should either satisfy the requirements in 21 C.F.R. § 206.5 and contain “adequate directions” for layman use, or they should satisfy 21 C.F.R. § 201.100(c) and § 201.100(d) and contain “adequate information” for all “intended uses”¹¹² based solely on the drug’s approved prescribing information.¹¹³ Under this regulatory framework, then, the Agency contends that even truthful and non-misleading information may not be communicated if it relates to an unapproved use.¹¹⁴ As described above, such a limitation on truthful and non-misleading information restricts the communication of information with valuable public health benefits and infringes upon manufacturers’ First Amendment rights to convey this information. We thus encourage FDA to modify its regulations to provide that such information may be communicated.

Specifically, FDA should adopt a savings clause in 21 C.F.R. § 201.100 to provide that statements that are based on scientifically- and statistically-sound methodologies and truthful and non-misleading information are not prohibited, regardless of whether the information establishes a new intended use that would otherwise require adequate information be provided through the approved prescribing information. Such a savings clause would mitigate the First Amendment

¹¹⁰ 21 C.F.R. § 201.100(c).

¹¹¹ 21 C.F.R. § 201.100(c).

¹¹² See 21 C.F.R. § 201.128 (defining “intended use” as “the objective intent of the persons legally responsible for the labeling of drugs,” as determined by “expressions” or “circumstances surrounding the distribution of the article”).

¹¹³ Recent amendments to the “intended use” definition clarify that a manufacturer’s knowledge that an approved product is used by physicians for unapproved uses is not in and of itself evidence that the manufacturer intends to market its product for an unapproved use. However, FDA’s reliance on an objective evaluation of the totality of the evidence still permits knowledge of a product’s use to be used as evidence of intended use beyond those approved in FDA labeling. See Clarification of When Products Made or Derived From Tobacco Are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses,” Final Rule, 82 Fed. Reg. 2193 (Jan. 9, 2017).

¹¹⁴ Superseding Misdemeanor Information, *United States v. Caronia*, No. 06-00229 (E.D.N.Y. Aug. 19, 2008) (describing the charge of misdemeanor misbranding through off-label promotion).

and policy concerns raised by the current regulatory framework, which FDA interprets to present an absolute bar for truthful and non-misleading communications of information not included in the approved prescribing information. The savings clause would also conform with the recent FDA draft guidance documents, which expressly permit communication of information outside of the approved prescribing information.¹¹⁵

C. Further Regulatory and Policy Changes

Although FDA's request for comments in this proceeding does not focus on core scientific exchange, we note that there are related concepts in FDA policies and regulations that also require modification in light of the public health benefits to a robust exchange of truthful and non-misleading information, as well as constitutional protections that extend to these communications. Current law fosters scientific discourse and debate in various settings, such as scientific presentations or other scientific communications during major medical association conferences and publication of peer-reviewed scientific and medical journal articles. As FDA notes, these forms of scientific communications fall outside of FDA's regulation and enforcement. However, certain prior FDA guidance includes recommendations that are too restrictive. We thus encourage FDA to include review of its guidance documents as part of its larger review of the regulatory framework governing manufacturer communications.

For example, FDA has recognized that sharing reprints of peer-reviewed scientific or medical journal articles reporting clinical research about alternative uses of approved drugs serves important public health and policy goals. While FDA's guidance permits dissemination of peer-reviewed reprints to health care professionals,¹¹⁶ certain of FDA's recommended practices restrict truthful and non-misleading communication with health care professionals and ultimately risk delaying the provision of timely, educational, and accurate information to health care professionals about certain unapproved uses, many of which are medically accepted and indeed even the standard of care for certain diseases. For instance, in addition to distributing reprints of journal articles about their medications, pharmaceutical company representatives

¹¹⁵ See Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities, Draft Guidance, 82 Fed. Reg. 6568 (Jan. 19, 2017) (permitting the communication to payors of information "related to an approved indication," including "the disease or condition, manifestation of the disease or condition, or symptoms associated with the disease or condition in the patient population for which the drug is indicated in the FDA-approved labeling"); Medical Product Communications That Are Consistent With the FDA-Required Labeling, Draft Guidance, 82 Fed. Reg. 6575 (Jan. 19, 2017) (permitting the communication of information "consistent with FDA-required labeling" based on how the information "compares to the information about those conditions of use in the FDA-required labeling," whether it increases the potential for harm to health, and whether the directions for use enable the product to be safely and effectively used under the conditions in the communication).

¹¹⁶ See FDA, *Draft Guidance for Industry on Distributing Scientific and Medical Publications on Unapproved New Uses--Recommended Practices* (Feb. 2014), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387652.pdf>; see also, e.g., FDA, *Draft Guidance for Industry on Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products--Recommended Practices* (June 2014), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400104.pdf>.

should be able to discuss these articles with health care professionals in a truthful and non-misleading manner. Further, company representatives should be able to distribute truthful and non-misleading summaries of information presented in such reprints, as the Court in the *Amarin* case also allowed. We encourage FDA to provide that such communications are permissible under current law, particularly as FDA works toward finalized guidance on good reprints practices.

Similarly, FDA should take steps to clarify that sponsors of new drugs or new indications in the pre-approval process may also communicate truthful and non-misleading information. As the recent draft guidance on payor communications reflects, early and robust communications with payors and population health decision-makers is critically important to budgeting and ensuring that patients have access to medicines.¹¹⁷ In this regard, however, FDA has adopted regulations for communications regarding investigational products that may chill such beneficial communications about a product prior to FDA approval. FDA's regulation at 21 C.F.R § 312.7 prohibits manufacturers from making "promotional claims of safety or effectiveness of the drug for a use for which it is under investigation," but does not prohibit "the full exchange of scientific information concerning the drug."¹¹⁸ There is considerable ambiguity surrounding the type of information that may be exchanged under this regulation. We encourage FDA to adopt an explicit savings clause that clarifies that pre-approval communications with payors and population health decision-makers are permitted if they are based on scientifically- and statistically-sound methodologies, and meet the truthful and non-misleading standard as articulated above and in the PhRMA-BIO Principles.¹¹⁹ While FDA's draft guidance on payor communications provides some clarity on pre-approval communications, we encourage FDA to adopt revisions to 21 C.F.R § 312.7 to further confirm the scope of permissible communications under FDA's current regulatory framework and guidance.

VI. Conclusion

PhRMA appreciates the opportunity to comment on the important issues presented in the FDA notice and First Amendment memo. For the reasons described, we believe that the First Amendment case law and sound policy mandate some refinements to the FDA framework. We believe those refinements can be accomplished in a manner that protects and preserves the important public health and safety gatekeeping role for the FDA. The PhRMA-BIO Principles document, and the safeguards included therein and described above, were carefully designed to balance all competing interests in a manner that we believe is more consistent with modern day

¹¹⁷ Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities, Draft Guidance, 82 Fed. Reg. 6568 (Jan. 19, 2017).

¹¹⁸ 21 C.F.R. § 312.7(a).

¹¹⁹ See Academy of Managed Care Pharmacy, AMCP Partnership Forum: Enabling the Exchange of Clinical and Economic Information Pre-FDA Approval, *J Manage Care Spec Pharm*, 2017 Jan;23(1):105-112. (stating that "[o]ver the past several years, organizations that make health care coverage decisions, including those that set copayments, premiums and formulary placement, have expressed a need for receiving this information prior to approval, as long as appropriate safeguards existed to prevent this information from reaching unintended entities").

First Amendment jurisprudence and health care delivery models. We value our relationship with FDA, and look forward to continuing to work with FDA on these important matters.

Respectfully submitted,

_____/s/_____
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General Counsel

_____/s/_____
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_____/s/_____
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Appendix A

Attached.

PRINCIPLES ON RESPONSIBLE SHARING OF TRUTHFUL AND NON-MISLEADING INFORMATION ABOUT MEDICINES WITH HEALTH CARE PROFESSIONALS AND PAYERS



INTRODUCTION

In the era of data-driven medicine, where all parties seek more, not less, information about the safety, effectiveness, and value of treatments, fostering informed communications among all stakeholders is critical. Today, the wealth of information about medicines is more comprehensive and complex than ever before. Scientific knowledge and new findings go far beyond data sets produced from clinical trials, often are outside the scope of the parameters established by Food and Drug Administration (FDA) regulations, and often outdate the FDA-approved labeling. In addition to information in the approved labeling for medicines, biopharmaceutical companies continually generate and collect important data and analyses that can benefit patient care and enhance the efficiency of our health care system.

To exercise sound medical judgment in treating patients, health care professionals must understand the full range of treatment options, including both established and emerging information about available medications. Biopharmaceutical companies are uniquely positioned to help health care professionals achieve the best outcomes for patients, because companies can provide timely, accurate, and comprehensive information about both approved and unapproved uses of the medications they research, develop, and bring to patients. PhRMA, BIO and their members believe that the availability of a wider range of truthful and non-misleading information can help health care professionals and payers make better informed medical decisions for their patients, which in turn will benefit patients.

In order to support the best use of scientific information for patient care, PhRMA and BIO endorse these Principles on Responsible Sharing of Truthful and Non-Misleading Information About Medicines with Health Care Professionals and Payers. These Principles are intended to form the basis for defining new and clear regulatory standards governing responsible, truthful and non-misleading communications to inform health care professionals about the safe and effective use of medicines. The Principles pertain primarily to data and information outside of FDA-approved labeling, and are intended to establish responsible, science-based parameters for accurate and trusted information sharing.

KEY CONCEPTS OF THE PRINCIPLES INCLUDE OUR MEMBERS':

- **Commitment to Science-based Communication.** Communications should be based on analyses using scientifically- and statistically-sound methodologies. There are many types of data and analyses that are scientifically- and statistically-sound, and thus can support truthful and non-misleading communication about medicines. These include analyses that can improve patient care based on pharmacoeconomics, usage based on real world evidence, and post hoc analyses that focus on specific sub-populations.
- **Commitment to Provide Appropriate Context about Data.** Communications should clearly disclose appropriate contextual information about the data presented, including information about limitations of the data and the analyses conducted to prevent health care professionals and payers from reaching inaccurate conclusions or forming misimpressions about the efficacy or safety of a medicine.
- **Commitment to Accurate Representation of Data.** Limitations on communications should be based principally on ensuring that data are represented accurately, which includes disclosing limitations of the data and the scientific and analytical methodologies used. Communications and underlying information can be truthful and non-misleading without regard to the identity of the speaker.

Finally, robust scientific discourse is critical to scientific progress and advances in public health. Current law fosters scientific discourse and debate in various settings, such as scientific presentations or other scientific communications during major medical association conferences and publication of peer-reviewed scientific and medical journal articles. These forms of scientific communications fall outside of the FDA's oversight, and the Principles described here do not apply to them.

PRINCIPLES:

1. **Commitment to Accurate, Science-Based Communications**

Biopharmaceutical companies should communicate accurate information based on established medical and scientific methodologies. Companies should not share information unless it is based on scientifically- and statistically-sound methodologies.

SCENARIO 5 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

2. **FDA-Approved Labeling is a Primary Source in Sharing Information with Health Care Professionals About Medicines**

Communications about a medicine are truthful and non-misleading if they accurately and fairly describe information contained in its FDA-approved labeling. Companies should continue to use the FDA-approved labeling as a primary source in communicating to health care professionals about approved medicines. In communicating information from the FDA-approved labeling, companies must fairly describe both the efficacy and the safety profile of the medication, including important risks.

SCENARIO 14 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

3. **Companies Should Provide Scientific Substantiation if Shared Information is Not Contained in FDA-Approved Labeling**

Health care professionals rely on a wide range of data from a variety of sources to inform patient care. There are many types of data and analyses that are scientifically- and statistically-sound, and thus can support truthful and non-misleading communication about medicines. When communicating evidence based on clinical research other than in the form of adequate and well-controlled trials, companies should disclose sufficient information for the audience to understand the specific research and any limitations. It is particularly important for a company to portray accurately the applicable methodologies and data, which can include limitations in the study methodology and/or statistical results.

To help ensure that physicians and other trained health care professionals can appropriately weigh data that are not contained in the FDA-approved labeling for a drug, companies should make appropriate disclosures, including the following:

- The design and implementation of the study (including the patient populations included and excluded, the total number of patients evaluated, the length of the study, the primary and key secondary endpoints, and whether the study met those endpoints);
- Significant limits on the study methodology (e.g., whether and how the study methodology may be subject to potential sources of bias or other weaknesses);
- The statistical analysis plan;
- Limitations of the statistical results (e.g., the statistical significance of the data and whether the results can be generalized); and
- Other relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence.

Companies should disclose information as part of the oral or written communication sufficient to ensure that the communication is not misleading, and may direct health care professionals to a website or other source for more comprehensive information.¹

SCENARIOS 1 AND 2 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

4. **Additional Science-based Information from Sources Other Than FDA-Approved Labeling Helps Health Care Professionals and Payers Make Informed Decisions for Patients**

PhRMA, BIO and their members believe that the availability of a wider range of truthful and non-misleading information can help health care professionals and payers make better informed medical decisions for their patients, which in turn will benefit patients. Sources for such additional information include:

¹Such information may be password-protected to ensure that it may be accessed only by health care professionals.

- Data from randomized, controlled clinical trials;
- Pharmacoeconomic information;
- Post hoc analyses of clinical trial results, including sub-population analyses;
- Observational data and real world evidence; and
- Physician treatment guidelines²

PhRMA, BIO and their members can and should be able to communicate truthful and non-misleading information from these additional sources in a responsible manner. To ensure that health care professionals are able to make informed judgments based on the information provided, it may be necessary for the company to include a variety of disclosures and disclaimers. Therefore, when communicating information not in the FDA-approved labeling, companies should include contextual information that allows health care professionals fully and fairly to assess the significance of, and any limitations upon, the evidence presented.³ The contextual information provided by a company to ensure that a communication is truthful and non-misleading will vary based on several factors, including:

- The complexity of the information presented;
- The underlying scientific research supporting it;
- The existence of other research reaching different results; and
- The sophistication of the audience;

SCENARIOS 1-4 AND 7 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

5. Communications Should Be Tailored to the Sophistication of the Intended Audience

To communicate information in a truthful and non-misleading manner, biopharmaceutical companies should carefully consider the level of sophistication of the intended audience. For example, the training and experience regarding the subject addressed in the communication may vary among different types of health care professionals (e.g. ranging from general practitioners to health care professionals who work for payers and routinely review pharmacoeconomic analyses). Companies can and should determine the sophistication of the health care professionals who receive the companies' communications. Companies can and should tailor their communications based on that determination, providing more detailed contextual information for audiences that require additional background to evaluate the relevance and significance of the information presented.

SCENARIO 10 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

6. Science-based Information About Alternative Uses of Medicines Can Improve Health Care Decision-Making

There exists a wealth of important information about the approved uses of medicines. In addition, respected third-parties, such as national medical associations and compendia services, often publish compendia or treatment guidelines that recommend or describe uses of medicines to treat patients outside the FDA-approved labeling. Recognizing the public health value of such alternative uses of approved medicines, public and private insurers often reimburse for them, and an estimated 21 percent of prescriptions by health care professionals are for alternative uses of approved medicines.

Biopharmaceutical companies are expected to collect the most comprehensive and up-to-date clinical information about their medicines—including information on alternative uses beyond the approved indication or dosing. Because this information can help health care professionals make informed decisions about the best treatments for their patients, companies should be able to communicate about such medically accepted alternative uses in a truthful and non-misleading manner.

² Several of these sources of information are described in greater detail in Appendix A.

³ Biopharmaceutical companies should not be hesitant to publish new scientific developments; however, publication should not be a prerequisite to truthful and non-misleading communications about such new developments.

Furthermore, companies must be able to participate fairly in the medical and policy discourse about the appropriate use of their medicines – even if communications include information outside of the FDA-approved labeling. This is especially true when other stakeholders conduct research about a company’s product and communicate about it publicly. In such instances, the company should be able to respond in a truthful and non-misleading manner.

As with any other type of information not included in FDA-approved labeling, company communications about alternative uses of medicines should disclose sufficient information to permit health care providers to assess the significance of, and limitations on, the evidence supporting such alternative uses. When communicating about alternative uses of medicines to appropriately sophisticated audiences, companies should disclose, among other things:

- The regulatory status of the medicine (e.g., FDA-approved, FDA-approved for another use, not FDA-approved);
- The underlying scientific research supporting such alternative uses (e.g., one or more adequate and well-controlled clinical trials, scientifically-sound post hoc analyses of clinical trial results (including sub-population analysis), open label extensions of clinical trials, registration studies, real-world evidence, etc.);
- Limitations on study methodologies and resulting data; and
- The relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence.

Companies should include these disclosures with the oral or written communications.

SCENARIOS 6, 7, AND 8 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

7. Communicating with Payers About New Medicines and New Uses of Approved Medicines Facilitates Patient Access Upon Approval

Prompt access to new medicines, or to approved medicines with new indications, can be critical to patient care. This is particularly true when the new medicine or new indication is a breakthrough in treating a life-threatening disease or where the new drug is safer or more effective than existing treatment. Therefore, biopharmaceutical companies should be able to communicate certain information to insurance providers, pharmacy benefit managers and government health care programs, so they may consider whether to reimburse for the medicine and account for the potential cost of the new medicine. For example, a company should be able to describe the company’s research and development pipeline, the status of any FDA applications, the anticipated use(s) of the company’s pipeline products, relevant data from the clinical trials, applicable treatment guidelines, and pharmacoeconomic information. Any such description should make clear that the FDA has not yet approved the drug, the particular use, or the information being conveyed.

SCENARIOS 9, 10, AND 11 IN APPENDIX B ILLUSTRATE THIS PRINCIPLE.

8. Real-World Evidence Based on Patient Experience and Pharmacoeconomic Information Can Improve Understanding of Health Outcomes and Costs

Many health care organizations, including insurance providers, managed care organizations, pharmacy benefit managers, government health care programs, hospital systems, accountable care organizations, and integrated delivery networks make decisions on health care delivery across large populations. These organizations possess patient data relating to real-world uses of approved medicines, conduct their own research on such data, and may wish to collaborate with biopharmaceutical companies to determine the overall impact of medicines in specific patient populations. Real-world evidence—evidence derived from data gathered from actual patient experiences—can help improve our understanding of disease and health.⁴ For example, modeling long-term endpoints and effects on different populations can help payers and health systems understand expected benefits for patients.

So long as the research methods are sound and well-described, companies should be able to communicate truthful and non-misleading

⁴ See Robert M. Califf & Rachel Sherman, What We Mean When We Talk About Data (Dec. 10, 2015), available at http://blogs.fda.gov/fdavoices/index.php/2015/12/what-we-mean-when-we-talk-about-data/?source=govdelivery&utm_medium=email&utm_source=govdelivery.

information about analyses of real world data with payers and health systems. These organizations are very sophisticated about such analyses and can evaluate the significance and limitations of the results.

SCENARIO 12 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

9. Commitment to Share Information Published in Scientific or Medical Journals

FDA has recognized that sharing reprints of peer-reviewed scientific or medical journal articles reporting clinical research about alternative uses of approved drugs serves important public health and policy goals. FDA therefore has issued recommendations concerning “Good Reprints Practices” permitting dissemination of peer-reviewed reprints to health care professionals. PhRMA, BIO and its members support FDA’s continued focus on providing concrete guidance regarding the types of disclosures and other steps manufacturers should take to disseminate information about unapproved uses without risking regulatory or even criminal enforcement. Nevertheless, certain of FDA’s recommended practices would restrict truthful and non-misleading communication with health care professionals and ultimately risk delaying the provision of timely, educational, and accurate information to health care professionals about certain unapproved uses, many of which are medically accepted and indeed even the standard of care for certain diseases. For example, biopharmaceutical companies should be able to share journal articles about research that they sponsor about their own medications as well as reprints of research sponsored by others.

The same public health and policy justifications set forth in the Good Reprint Practices also apply to oral or written summaries of such reprints. Therefore, in addition to disseminating reprints, company representatives should be able to describe information presented in such reprints. To help ensure that physicians and other trained health care professionals can appropriately weigh such oral or written summaries of data contained in a medical or scientific reprint, companies should include appropriate disclosures, including the following:

- Accurate and balanced information about the approved product labeling (including the indication, limitations of use, efficacy and safety data described therein);
- The type of research that is the subject of the reprint (including the study design, method of analysis, and appropriate, context-specific disclosures regarding the limitations with retrospective meta-analysis);
- The results reported in the reprint, including the statistical significance and confidence intervals of each result;
- Information about the source of funding for the reprint; and
- Other relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence.

SCENARIO 13 IN APPENDIX B ILLUSTRATES THIS PRINCIPLE.

⁵The company should disclose the trial design and analytical methodology used in the study, including any limitations of the methodology. The company should not simply direct the health care professional to the reprint for a description of the study design and analytical methodology.

APPENDIX A

TYPES OF INFORMATION ABOUT MEDICINES

In addition to information contained in the FDA-approved labeling for medicines, biopharmaceutical companies continually generate and collect the following types of information about medicines. Responsible sharing of information, including the following categories, can improve patient care and the efficiency of the health care system:

- **Data from randomized, controlled clinical trials** – Scientifically rigorous and FDA-regulated clinical studies, including Phase I - IV clinical trials, evaluate pre-specified endpoints under a clearly defined analysis plan. Clinical trials are among the most reliable tools in evaluating the safety and effectiveness of medicines. The results often are independently peer-reviewed and published; however, only a fraction of the data from these studies is contained in the FDA-approved labeling.
- **Post hoc analyses, including sub-population data** – Randomized controlled clinical trials and observational studies often collect information on the safety and effectiveness of medicines in subpopulations, including specific gender and ethnic cohorts. The analysis of these data often occurs after the conclusion of the trial, as the subpopulation data may not have been pre-specified endpoints or part of the original plan of analysis. If the trial has met its primary endpoint, this specific sub-population information can help health care professionals develop treatment strategies based on more precise safety and efficacy data for a particular cohort of patients.
- **Observational data and real-world evidence** – A growing amount of information is gathered from claims data, electronic medical records, or patient registries that can provide specific and up-to-date information about the actual use of approved medicines. Observational data, comparative effectiveness research, and other real-world evidence can help clinicians understand how medicines perform across a diverse patient population outside of controlled trials. Such data may reflect prescribing patterns in different clinical practice settings, alternative doses, and differing durations of treatment, as well as comparisons between two or more therapies.
- **Pharmacoeconomic information** – Health care economic data demonstrating the value of medicines can be obtained from clinical trials, observational studies, reviews of medical record databases, or other predictive modeling techniques. This information can include analyses of outcomes from patient population data sets, cost-effectiveness models, and budget models. Such information can help improve the efficiency of patient care and of the health care system, as well as better inform payers regarding the budget implications of coverage decisions.

APPENDIX B

EXAMPLES OF RESPONSIBLE SHARING OF TRUTHFUL AND NON-MISLEADING INFORMATION IN VARIOUS COMMUNICATION SETTINGS

The following hypothetical scenarios are meant to illustrate how companies may apply the Principles described in this document under new regulatory standards governing responsible information sharing with health care professionals. These scenarios demonstrate that responsible sharing of truthful and non-misleading information is highly fact-specific.

Scenario 1: After receiving approval for a drug indicated for the reduction of chemotherapy-induced nausea, a biopharmaceutical company conducts a Phase IV randomized, controlled clinical trial using pre-specified clinical endpoints to evaluate the average duration of efficacy for the approved course of therapy. This is a new efficacy measure, not included in the FDA-approved labeling. The study meets its primary and secondary endpoints. FDA has not expressed views on the study, and the company has not sought to include the new data in the labeling. No randomized, controlled studies conflict with this study. To communicate the results of this trial to prescribing physicians in a truthful and non-misleading manner, the company should disclose, among other things, (a) the study design (including the number of patients in each study arm, the inclusion and exclusion criteria, the pre-specified primary and key secondary endpoints, and whether the study met those endpoints) and the statistical significance and confidence interval of the results on the key endpoints; (b) pertinent safety results; (c) that the information is based on only one randomized, controlled trial; and (d) that the study is not included in the product's package insert and that FDA did not consider it in approving the product. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principles 3 and 4.

Scenario 2: After receiving approval for a drug's use in adult patients, a biopharmaceutical company submits a supplemental NDA for an additional use in children. The company conducts a randomized, controlled clinical trial on the second use, and the study meets the pre-specified endpoints. FDA acknowledges that the clinical trial demonstrated the safety and efficacy of the drug in the tested population, but there will be a delay with an update to the approved labeling addressing these additional data. Another study conducted by independent investigators presents contrary evidence about the efficacy of the drug in children. To communicate the results of the trial it conducted to prescribing physicians in a truthful and non-misleading manner before the FDA approves updated labeling, the company should disclose, among other things: (a) the study design, number of patients studied, and key exclusion criteria; (b) the results of the pre-specified primary and key secondary endpoints (including p values and confidence intervals); (c) pertinent safety results; (d) the existence of only one randomized, controlled trial supporting the information; (e) the lack of any reference to the study in the labeling; (f) regulatory status; and (g) other evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence (including p values and confidence intervals). The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principles 3 and 4.

Scenario 3: A drug for treating allergic rhinitis receives FDA approval based on a composite efficacy endpoint that measured patients' total symptom improvement over six individual symptoms. The three pivotal clinical studies that formed the basis for approval measured efficacy in the individual symptoms as tertiary endpoints. The efficacy results for four of the six individual symptoms were statistically significant. Because the studies did not designate individual symptom scores as secondary endpoints, FDA does not permit the manufacturer to include these data in the labeling, but has not otherwise expressed views on these results. To communicate this information to prescribing physicians in a truthful and non-misleading manner, the company should disclose, among other things: (a) the number of patients studied, as well as the p values and confidence intervals for all six of the symptoms evaluated; (b) the omission of individual symptom efficacy as a primary or secondary end point of the study;

(c) the prospective definition of and pre-specified analysis plan for these tertiary endpoints; (d) the inclusion or absence of a prospectively planned adjustment to control for false positives or other forms of potential bias; (e) any other risk of potential bias regarding this data; (f) pertinent safety results; and (g) FDA's decision not to include this data in the product labeling and the reasons why. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 4.

Scenario 4: A biopharmaceutical company manufactures a drug approved for treating symptoms of Parkinson's disease in adults. The company conducts a methodologically sound, post hoc analysis of data from the pivotal clinical trials to measure the effect of the medication on the individual symptom of pain. Pain was among the symptoms measured as part of a composite primary endpoint; however, the studies did not pre-specify individual symptom scores as a secondary or tertiary endpoint. No published studies present contradictory evidence. To communicate the results of this post hoc analysis to prescribing physicians in a truthful and non-misleading manner, the company should disclose, among other things: (a) the omission of the effect of the drug on pain as a pre-specified primary, secondary or exploratory endpoint; (b) the post hoc nature of the analysis, and its consequent failure to meet FDA's standard for an adequate and well-controlled study; (c) the pre-specified primary endpoint(s) and the results; (d) the methodology for the post hoc analysis, including (i) whether the post hoc analysis was designed to test a pre-specified endpoint in accordance with a pre-specified analysis plan, and (ii) how the study controlled for confounding factors; (e) the results of the post hoc analysis, including the statistical significance and confidence intervals; (f) pertinent safety results shown in the post hoc analysis; (g) any other risks of bias not already specified with a retrospective data analysis; and (h) the post hoc analysis is not included in the product's labeling and FDA did not consider this analysis in approving the product. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 4.

Scenario 5: A biopharmaceutical company conducts an open-label study in a population of 12 patients to evaluate the safety and efficacy of one of its oncology drugs for its approved indication. The study does not meet its primary safety end-point. Although the study meets one of several secondary efficacy endpoints, the result is not statistically significant. Because information about the one successful secondary endpoint is not based on scientifically- or statistically-sound methodologies, the company should not communicate this information outside of recognized contexts of scientific discourse and debate, which are outside of the scope of these Principles. This scenario implicates Principle 1.

Scenario 6: A biopharmaceutical company obtains FDA approval of a drug for treating lung cancer. The company conducts an adequate and well-controlled clinical trial for the product to determine whether it is a safe and effective treatment for pancreatic cancer. The clinical trial includes 100 patients. Of those 100 patients, half are tested with the company's product and the other half are tested with the standard of care product. In the standard of care arm, 50% of the patients achieve survival rates of more than one year, and the other 50% survive between six months and one year. In the testing arm of the study, 80% of patients achieve survival rates of more than one year and 20% of the patients survive for more than six months. Additionally, some patients in the testing arm develop liver and kidney failure, while none of the patients in the standard of care arm suffers those side effects. To communicate the results of this trial to a clinical practice guideline committee in a truthful and non-misleading manner, the company should disclose all of the above statistical information about safety and include appropriate descriptions and limitations of the study. This scenario implicates Principle 6.

Scenario 7: At a medical conference, a biopharmaceutical company hosts a product theater to describe new scientific research relating to one of the company's products. The new research includes information from post hoc analyses of sub-population data collected under the randomized, controlled clinical trials that formed the basis for the product's approval. This sub-population analysis was not a pre-specified endpoint of the trials. Neither the company nor any independent investigators have conducted randomized, controlled clinical studies evaluating the efficacy and safety of the drug on this sub-population. The FDA has not reviewed or expressed an opinion about the company's new research. To communicate this information at the product theater

in a truthful and non-misleading manner, the company should disclose, among other things: (a) the omission of the sub-population analysis as a pre-specified primary, secondary or exploratory end-point; (b) the post hoc nature of the analysis and its consequent failure to meet FDA's standard for adequate and well-controlled research; (c) the pre-specified endpoint(s) and the results of the study in the overall study population; (d) the methodology for the sub-population post hoc analysis (including how the study controls for confounding factors); (e) all the results of the post hoc analysis (including p values and confidence intervals); (f) any risk of various types of bias not already described; (g) pertinent safety results shown in the post hoc analysis; (h) any warnings and precautions in the product labeling that specifically apply to this sub-population; and (i) the absence of any FDA review of or opinion about this new research. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principles 4 and 6.

Scenario 8: A biopharmaceutical company sponsored a phase 3 trial to expand the indication of one of its approved drugs to include rheumatoid arthritis (RA). Members of the company attend a physician medical association rheumatology conference. A principal investigator for the clinical trial sponsored by the company makes a podium presentation at the conference summarizing the results of the trial, and scientific staff of the company discuss the results with conference attendees. The scientific discourse described here is not subject to these Principles and should not be regulated by the FDA.

Scenario 9: In collaboration with a large health insurer, a biopharmaceutical company has evaluated the rate of hospitalizations for patients who use the company's cardiovascular drug for its indicated use, compared with the rate of hospitalizations for patients who use a competitor's drug, based on real-world evidence from the insurer's electronic medical records for over 200,000 adult patients nationwide. The data demonstrate that both the company's drug and the competitor's drug significantly reduced the rate of hospitalizations in patients ages 50-65. However, the competitor's drug demonstrated a higher rate of hospitalizations in this population. After communicating accurate and balanced information about use of the company's product in accordance with the approved labeling, to communicate this real-world data to additional payers in a truthful and non-misleading manner, the company should disclose, among other things: (a) the observational nature of this study, based on a review of the insurer's member data; (b) the study methodology and method(s) of statistical analysis; (c) any significant limitations of the data or the databases used; (d) the results of the study for both the manufacturer's drug and the competitor drug; (e) any pertinent safety results of this observational study; and (f) any risk of bias not otherwise described above. The company should summarize these disclosures in the oral or written communications, and can refer payers to a website for more comprehensive information about the observational study. This scenario implicates Principles 7 and 8.

Scenario 10: A biopharmaceutical company contacts a major health plan and requests an opportunity to present information regarding its oncology product pipeline. The company's slide presentation includes a timeline showing agents that are in Phase 3, Phase 2, and Phase 1 of development, with a one-page description of each study, including the study design and primary and secondary end points. The presentation is for the pharmacy and therapeutics committee of the health plan ("P&T Committee"), whose members include physicians and doctors of pharmacy. This is a highly sophisticated audience. The respective descriptions of the studies include results of primary and secondary endpoints and statistical significance but do not make statements that any of the drugs has been determined to be safe or effective. To communicate top-level pipeline information to this audience in a truthful and non-misleading manner, the company should disclose, among other things: (a) the lack of FDA approval; (b) the possibility that FDA will not approve some agents in the pipeline; and (c) any material safety risks identified in the clinical studies conducted to date. This scenario implicates Principles 5 and 7.

Scenario 11: A biopharmaceutical company has submitted to FDA its NDA for an investigational oncology drug and expects approval within nine months. The company has scheduled meetings with the P&T committees of several pharmacy benefit managers and health plans to inform them that the product likely will be available within the year and to request that they consider placing it on their formularies promptly upon approval. To communicate information about the anticipated product indication, any limitations of

use, and the safety and efficacy data submitted to FDA as part of the application for approval in a truthful and non-misleading manner, the company should disclose, among other things: (a) the current status of the NDA; (b) the type of research that supports the safety and efficacy for the use of the product under consideration by FDA (with appropriate, context-specific disclosures regarding the specific research); (c) any FDA opinion on the sufficiency of the evidence; and (d) other relevant evidence that is necessary to an informed medical judgment, including any peer-reviewed contrary evidence. The company should make these disclosures as part of the oral or written communication. This scenario implicates Principle 7.

Scenario 12: A biopharmaceutical company contracts with a payer to acquire de-identified patient population data in exchange for a fair market value payment. The company then conducts a sub-group analysis on that data set. The company's analysis shows a correlation between the manufacturer's product and progression-free survival in African American patients. To communicate information about this sub-group analysis to the payer who provided the data, as well as to other payers, in a truthful and non-misleading manner, the company should disclose, among other things: (a) the study's reliance on a retrospective review of real-world evidence; (b) the observational nature of the study and the absence of a control group, resulting in the study's failure to meet FDA's standard for adequate and well-controlled research; (c) the absence of any FDA evaluation of the results; (d) the methodology for the sub-population post hoc analysis (including how the study controls for confounding factors); (e) any risk of various types of bias not already described; (f) pertinent safety results of this analysis; and (g) any warnings and precautions in the product labeling that specifically apply to this sub-population. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 8

Scenario 13: Independent investigators have conducted a retrospective, meta-analysis regarding the safety and tolerability of a biopharmaceutical company's drug based on results from various randomized clinical trials conducted world-wide. The results of this meta-analysis are published in a peer-reviewed journal in accordance with all of the criteria set forth above. The company has reviewed the reprint and believes the analytical methodologies used by the investigators are scientifically sound. The company could distribute reprints of this journal article to health care professionals. In addition, to communicate information about the content of the reprint during sales representative calls to health care professionals in a truthful and non-misleading manner, the company should disclose, among other things: (a) accurate and balanced information about the approved product labeling (including the indication, limitations of use, efficacy and safety data described therein); (b) the type of research that is the subject of the reprint (including the study design, method of analysis, and appropriate, context-specific disclosures regarding the limitations with retrospective meta-analysis); (c) the results reported in the reprint, including the statistical significance and confidence intervals of each result; and (d) other relevant evidence that is necessary to an informed medical judgment, including peer-reviewed contrary evidence. The company should summarize these disclosures in the oral or written communications, and can refer the health care professional to a website for more comprehensive information about the study. This scenario implicates Principle 9.

Scenario 14: A biopharmaceutical company obtains FDA approval for a drug to treat cystic fibrosis. The Phase III pivotal study data are incorporated in the approved labeling and demonstrate statistically significant improvement in lung function. The data also show serious adverse events in 10% of the patients, including liver and kidney failure. The company can communicate the labeled data on improvement of lung function in discussions with health care professional, as well as in written materials, but also must include the information about safety risks in all such discussions and materials. All communications about the product should fairly balance the efficacy information with the risk information. This scenario implicates Principle 2.

Scenario 15: A large pharmacy benefit manager ("PBM") releases the results of comparative effectiveness research ("CER") that was based on a meta-analysis of various other studies that had previously been performed by payer-affiliated groups. The CER analysis supports using treatment options other than a biopharmaceutical company's product. The affected company has conducted its own health care economic analyses and outcomes research. The data from the company's research strongly refute the PBM's

CER. The company should be able to respond to the PBM's public statements about the company's drug with information from the company's research. To communicate such information in a truthful and non-misleading manner, the company should disclose, among other things: (a) the study methodology and method(s) of statistical analysis; (b) any significant limitations of the data or the databases used; (c) the results of the study for the manufacturer's drug and any competitor drugs (if applicable); (d) pertinent safety results of this analysis; and (e) any risk of bias not otherwise described above. The company should summarize these disclosures in the oral or written communications, and can refer health care professionals to a website for more comprehensive information about the company's research. This scenario implicates Principle 4.

Appendix B**PhRMA analysis of 46 branded medicines covered in the National Comprehensive Cancer Network Drugs and Biologics Compendium and the Micromedex DRUGDEX***Methods*

We identified a list of 46 recently FDA approved (original or new indication) oncology medications. Medicines used in combination with devices or with generic alternatives were not included in this list.

The Centers for Medicare & Medicaid Services (CMS) recognizes five compendia under the Social Security Act Section 1861(t)(2)(B)(ii)(I). Uses of drugs and biologics supported in these CMS-recognized compendia are recognized as “medically accepted indication,” if certain criteria are met. Two of these compendia are the Micromedex DRUGDEX and the NCCN Drugs and Biologics Compendium. We queried each compendium for the same 46 medications identified in the process above.

Next, we created a database including brand and generic medication names, FDA labeled indication, manufacturer, New Drug Application (NDA)/Biologics License Application (BLA) number, compendium recommendation, and a series of variables to describe how the compendium recommendation differs or does not differ from the FDA approved label (see **Table 1**).

Table 1. Variables to Describe and Quantify Differences between FDA-Approved Labels and Compendia Recommendations

Variable	Definition
Any Recommendation for Unapproved Use (<i>Binary variable</i>)	Does the compendium make any off-label recommendation?
Unapproved Indications/Disease States (<i>Count variable</i>)	Does the compendium recommend use of the medication in another tissue/disease? If yes, count tissues/diseases recommended beyond label.
Additional Medicine Combinations Mentioned (<i>Binary variable</i>)	Does the compendium recommend the medication be used in combination or before/after other medications not mentioned in the label?
Alternate Patient Populations/Subpopulations (<i>Binary variable</i>)	Does the compendium make recommendations on groups or populations not included in the label?
Alternate Disease Progression Mentioned (<i>Binary variable</i>)	Does the compendium recommend the medicine be used in different progression stages or treatment lines than approved in the label?
Other conditions considered (<i>Binary variable</i>)	Does the compendium make recommendations on other off-label aspects to be considered for diagnosis and delivery? Can include patient preference for drug selection, conditions such as pregnancy, genetic test results, other diagnostic

results (e.g., Karnofsky performance score), or other.

Appendix C

2016 Ipsos Healthcare survey of board-certified oncologists

Methods

At the request of PhRMA, Ipsos randomly selected oncologists from a panel to participate in the study. A total of 202 surveys were collected from oncologists meeting the inclusion criteria in the table below. The sample included board-certified oncologists from across the United States in practice for between 2 and 30 years, who treat at least 5 patients a month.

Results

Use of Unapproved Treatments

- **69%** of oncologists (N=140) reported using treatments for unapproved uses
- Among these oncologists, the majority (**75%**) use an unapproved treatment infrequently (in 25% or less of their patients)
- The most common reasons for using unapproved treatments are when published evidence suggest efficacy (**95%** reported this as one of the top 3 reasons; **37%** reported this as the top reason)

Perceptions of unapproved treatments

- The most common sources of information for unapproved uses was the scientific literature (medical journals = 91%; abstracts/ conference proceedings = 76%).
- 78% of oncologists would find it helpful if more information about safety and efficacy of unapproved uses was available in their clinical practice. Of these oncologists, **85%** would be interested in receiving info from pharmaceutical manufacturers and **76%** would want access to info on unapproved uses sent to a colleague.
- **52%** of oncologists contacted a medical science liaison to talk about an unapproved use. Of these oncologists, **89%** found the information received useful.
- **77%** of oncologists reported they would be more likely to refer patients to a clinical trial if they had more info on unapproved uses

When receiving information on unapproved uses from a manufacturer, the most important factors to judge the validity of the information were:

- **Overall quality of study design** (**79%** reported this as one of the top 3 reasons; **37%** reported this as the top reason)
- **Quality of the target journal** (**71%** reported this as one of the top 3 reasons; **19%** reported this as the top reason)

Appendix D

PhRMA analysis of American College of Rheumatology Rheumatoid Arthritis (ACR RA) Guidelines and the Infections Disease Society of America (IDSA) Clinical Practice Guidelines on Hospital Acquired Pneumonia (HAP) and Ventilator Associated Pneumonia (VAP)

Methods

Clinical practice guidelines (CPGs) for rheumatoid arthritis (RA) and pneumonia are representative of CPGs, robust, and apply to a relatively large population of providers and patients. Where possible, we analyzed the medications specifically included as examples in these CPGs. When recommendations were made at a class level, we identified medicines with recent FDA approval (original or new indication). We also included medicines with generic versions in order to ensure we were capturing a representative sample from the classes recommended in the CPG. Thirteen (13) products were included in the RA analysis: Plaquenil, Azulfidine, Arava, Remicade, Orencia, Humira, Enbrel, Rituxan, Simponi, Cimzia, Actemra, Xeljanz, and Kineret. Fifteen (15) medicines were included in the HAP/VAP analysis: Vancocin hydrochloride, Zyvox, Zosyn, Maxipime, Fortaz, Primaxin, Merrem, Azactam, Cipro, Levaquin, amikacin, gentamicin, Coly-Mycin M, tobramycin, and polymyxin.

For each medication, we included in our database the FDA labeled indication, any pediatric approvals, relevant contraindications, warnings, precautions, dosage and administration, drug class, the CPG-recommended use, whether we identified any recommendation for unapproved use, and the differences between the FDA approved use and the CPG recommended use. We also included details such as manufacturer and approval date. Additional details of our analysis are available in the discussions below.

American College of Rheumatology Rheumatoid Arthritis (ACR RA) Guidelines

- The ACR RA does not list specific drugs, but rather makes recommendations on a class-level basis (e.g., anti-tumor necrosis factors [TNF], or disease modifying anti-rheumatic drugs [DMARDs]). As such, the CPG does not make recommendations for unapproved uses for specific drugs.
- ACR RA does, however, suggest the usage of unapproved combinations of products. This flows to a large extent from the multiple generations of RA products. The older DMARD drugs do not contain recommendations to use them in combination with the newer biologics; however, some of the newer biologics do mention the use of DMARDs in their labels.
- Overall, of 13 RA medications analyzed, 8 were associated with off-label recommendations in the ACR RA CPG.

Infectious Diseases Society of America (IDSA) CPGs on Hospital Acquired Pneumonia (HAP) and Ventilator Associated Pneumonia (VAP)

- Nothing is currently approved for VAP, so any recommendations towards that use would be considered off-label. Certain medications are recommended for HAP (i.e., nosocomial pneumonia), which are not included in their respective labels. We considered recommendations that differed from the label in terms of acquisition (i.e., nosocomial vs. community acquired pneumonia) to be off-label. We did not consider recommendations to be off-label if they addressed use for pneumonia or lower respiratory tract infections broadly.
- Overall, of 15 medications analyzed, we determined 7 to be associated with an off-label recommendation by IDSA.

Appendix E

2016 Health Strategies Group Survey of Payors and Physician Specialists

At the request of PhRMA, Health Strategies Group conducted quantitative survey research with a robust sample from key stakeholder constituencies. The survey was 15 minutes in length and results were double-blinded. Payers and providers were asked a series of questions about pipeline information, data not in the product label related to an approved indication, and data on unapproved uses. To help operationalize these concepts, several examples were provided to participants

Examples provided to characterize “*data not in the product label related to an approved indication*”

- Data on subgroups of patients within the approved population (e.g. race or gender specific information regarding a medicine that is approved in all adults)
- Data on outcomes not in the product labeling (e.g. long term outcomes related to the clinical trial endpoints on the product label)
- Pharmacoeconomic data
- Post market surveillance data
- Comparative effectiveness data

Examples provided to characterize “*data on unapproved uses*”

- Utilization for different diagnoses not listed in the product label (e.g., to treat schizophrenia if label is bipolar disorder)
- Utilization in patient populations not included in product label (e.g., to treat patients under 18, if label is in patients 18+)
- Utilization in different lines of therapy than indicated
- Utilization in an unapproved regimen / combination

Table 1. Study Sample and Exclusion Criteria

Payer Executives*	
National Managed Care Organizations (MCOs)	10
Regional MCOs	10
Pharmacy Benefits Managers (PBMs)	8
Integrated Delivery Networks (IDNs) ⁺	10
<i>Total</i>	38
Specialist Physicians[§]	
Cardiologists	20
Endocrinologists	19
Hematologists/oncologists	40
Neurologists	37
Psychiatrists	21
Rheumatologists	41
<i>Total</i>	178
Entire Sample	216

*Executives were asked to choose their level of involvement in the decision-making process for their organization on a scale of 1 (Not at all involved) to 7 (I am a key decision maker). Potential participants responding below 4 on this scale were screened from the survey.

+ IDNs were required to have an active Accountable Care Organization (ACO) program, population health program, or risk program to participate in the survey.

§Physicians were required to have 2-30 years in practice, see 200 or more patients in a typical month, have board certification, and spent at least 50% of their time in clinical practice (as opposed to research, academia, administration, or other functions).

Results

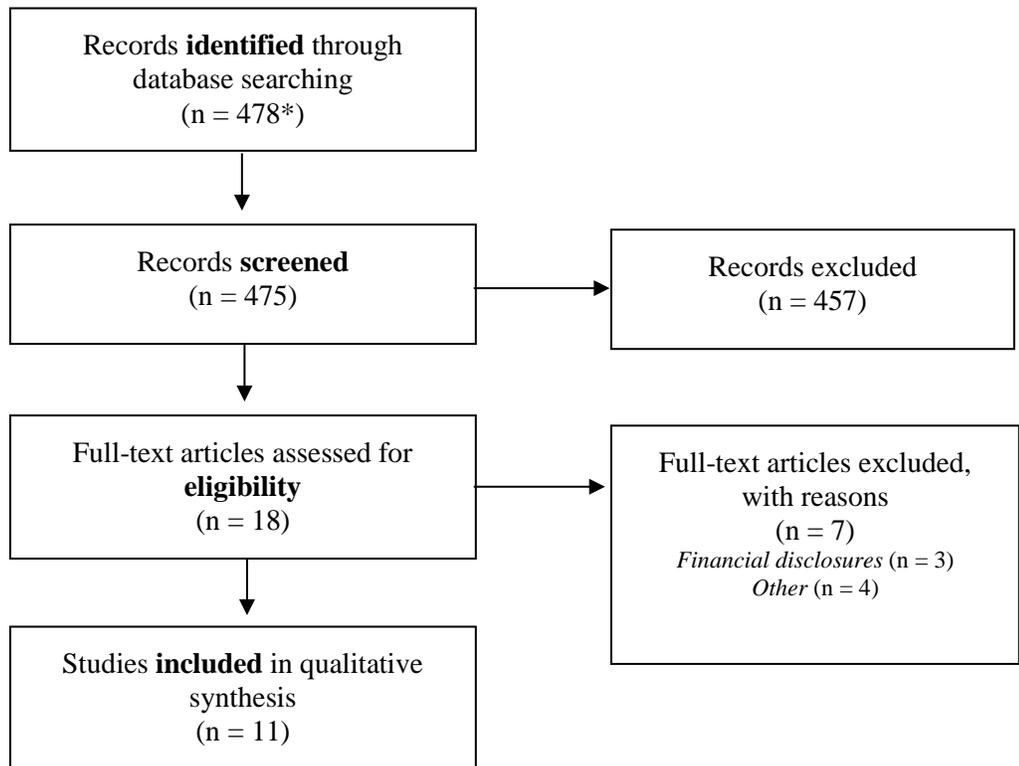
Receiving Information from Biopharmaceutical Companies

- Payers indicated interest in receiving more information from biopharmaceutical manufacturers, provided the information was scientifically sound; **86%** indicated this was true for data related to an approved indication, **82%** for unapproved uses, and **79%** for pipeline information.
- Specialty physicians also indicated interest in receiving more information from biopharmaceutical manufacturers, provided the information was scientifically sound; **83%** indicated this was true for data related to an approved indication, **85%** for unapproved uses, and **85%** for pipeline information.
- **79%** of payor executives surveyed agreed with the statement “*If companies were able to proactively share more information regarding unapproved uses of a product, I would still want to see the manufacturer take steps to have the use approved as an indication in the product labeling*” **13%** neither agreed nor disagreed and **8%** disagreed.
- **66%** of physician specialists surveyed agreed with the statement “*If I had more information about unapproved uses, I would more often refer patients to clinical trials that seek to develop evidence about the benefits of these uses.*” **28%** neither agreed nor disagreed with this statement and **6%** disagreed.

Appendix F

2017 Xcenda Systematic Literature Review: Peer-reviewed Evidence on Disclaimers and Disclosures

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram



*Some articles obtained through gray literature searching and from article references

Table 1. PubMed Search Strings

Search	Query	Items found
#1	Search (disclaimer OR disclosure)	47,786
#2	Search (lawsuit OR liabl* OR litigation OR legal OR (regulation AND policy))	524,189
#3	Search (pharmaceutical OR off-label OR supplement OR nutraceutical OR claim [tiab])	955,229
#4	Search (#2 AND #3)	21,848
#5	Search (#4 AND #1)	1,078
#6	Search (#5 AND Apply Filter: Publication date from 2007/01/01 to 2017/04/01)	475