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April 19, 2017

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

Re: Draft Guidance for Industry and Review Staff: Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers, Docket No. FDA–2016–D–1307, 82 Fed. Reg. 6568 (Jan. 19, 2017)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America ("PhRMA") appreciates the opportunity to submit these comments in response to FDA's Draft Guidance for Industry and Review Staff entitled "Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities/Questions and Answers" ("Draft Guidance"). 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.

PhRMA appreciates FDA's efforts to update existing guidance regarding manufacturer communications with payors. We also recognize that FDA has held a public hearing entitled "Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products"[1] and has issued separate draft guidance on manufacturer communications with healthcare professionals that are consistent with the FDA-approved labeling.[2] In addition to this comment letter, we are simultaneously submitting two additional comment letters. One responds to the hearing notice and FDA's accompanying Memorandum titled "Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products,"[3] and the other responds to the

[1] *See* 81 Fed. Reg. 60299 (Sept. 1, 2016).

[2] *See* FDA, Draft Guidance, Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers (Jan. 2017).

[3] FDA, Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products (Jan. 2017).

draft guidance on manufacturer communications with healthcare professionals that are consistent with the FDA-approved labeling.

In each of these contexts, FDA regulation of manufacturer communications should adhere to principles that ensure sophisticated audiences will benefit from accurate, data-driven information from all sources, including the companies that research and develop new medicines. In July 2016, PhRMA and the Biotechnology Innovation Organization ("BIO") jointly published principles, which affirm that communications should be based on analyses using scientifically- and statistically-sound methodologies, should clearly disclose appropriate contextual information, and should be tailored to the sophistication level of the intended audience.[4] Payors and population health decision-makers are highly sophisticated audiences that wish to obtain health care economic information ("HCEI") about both FDA-approved and investigational drugs for budget planning reasons, for coverage and patient access reasons, and to facilitate the development of value-based contracts. Therefore, these audiences are well positioned to evaluate information received from multiple sources, including biopharmaceutical manufacturers.

PhRMA understands FDA's important role in evaluating the safety and efficacy of new medicines and new uses of previously approved medicines. However, consistent with the above principles, we also recognize the critical need of payors and other population health decision-makers to receive the most current, accurate, and comprehensive information about the medicines that they cover and reimburse. Facilitating access to a broader range of truthful and non-misleading information about FDA-approved medicines and investigational products, including relevant clinical data and HCEI, can help payors make better informed decisions, which in turn benefits patients. Under the First Amendment, any appropriate regulation by FDA in this area thus requires a careful balancing of the interests at stake with appropriate recognition of the level of sophistication of the audience and the ability of the audience to review and comprehend HCEI and associated clinical and economic assumptions.

The Draft Guidance implements Section 3037 of the 21st Century Cures Act ("Cures Act"),[5] which amended Section 114 of FDAMA (Section 502 of the Federal Food, Drug and Cosmetic Act ("FDCA")) in several important respects. Each of these changes was intended to expand the scope of permitted communication of HCEI to entities involved in making coverage and reimbursement decisions. The changes reflect Congress's understanding that payors and similar entities are sophisticated audiences that can make informed judgments about information conveyed to them. In particular, the amended Section 502(a) protects communication of HCEI to:

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[4] *See* PhRMA and BIO, Principles on Responsible Sharing of Truthful and Non-Misleading Information about Medicines with Health Care Professionals and Payers (2016) [hereinafter "PhRMA-BIO Principles"].

[5] 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1105 (2016).[6] *See* 21 U.S.C. § 352(a). All further references to section 502(a) of the FDCA made throughout this comment letter refer to that section in its amended form.

> a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement . . . if the health care economic information relates to an [approved] indication . . . for such drug, is based on competent and reliable scientific evidence, and includes, where applicable, a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug.

The amended Section 502(a) further defines HCEI more broadly to include:

> any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug. Such analysis may be comparative to the use of another drug, to another health care intervention, or to no intervention.[6]

The Draft Guidance, in many respects, appropriately implements Congress's direction to broaden the scope of permitted communication of HCEI to sophisticated entities involved in coverage, reimbursement, and budgeting decisions. We appreciate FDA's efforts to provide concrete guidance regarding the types of disclosures and other steps manufacturers should take in order to provide HCEI to payors without risking enforcement. Nevertheless, the Draft Guidance in several important ways lacks clarity and reflects an overly restrictive approach to the regulation of manufacturer communications with payors. Therefore, in issuing final guidance, we ask that FDA implement the changes we describe below.

The remainder of this comment letter can be summarized as follows. Section I describes why it is vital that payors receive comprehensive and current information about the safety and effectiveness of medical products. Section II describes PhRMA's recommended changes to the Draft Guidance.

I. FDA's Guidance Should Encourage and Facilitate Manufacturers' Efforts to Provide Payors with Truthful, Non-Misleading Health Care Economic Information and Information About Unapproved Uses of Approved Products

In today's healthcare marketplace, patient access to life-saving and life-enhancing medicines often depends on coverage and reimbursement by payors. To make informed decisions about coverage and reimbursement, payors should receive comprehensive, high-quality, accurate, and up-to-date information about the products they might cover. Payors have expressed a need for this information with respect to approved products, unapproved uses of approved products, and entirely investigational products.

[6] *See* 21 U.S.C. § 352(a). All further references to section 502(a) of the FDCA made throughout this comment letter refer to that section in its amended form.

A. Payors Routinely Seek Health Care Economic Information About Approved Uses of Marketed Products

As FDA has recognized, manufacturers possess a wealth of information about the medicines they research, develop, and market, including HCEI. The Draft Guidance appropriately recognizes that payors routinely seek HCEI from manufacturers, and that HCEI "help[s] support their drug selection, formulary management, and/or coverage and reimbursement decisions on a population basis,"[7] and as FDA explains, such information helps payors "plan for and make coverage and reimbursement decisions far in advance of the effective date of such decisions."

A PhRMA survey confirms that payors want and use a broad range of comprehensive, well-researched, balanced, and credible information, both pre- and post-approval. The survey asked payors about their need for information outside of the FDA-approved labeling. Every payor surveyed—100% of them—responded that they consider additional data not in the product labeling related to an approved indication to be valuable information.[8]

A separate analysis of data collected through the Academy of Managed Care Pharmacy ("AMCP") eDossier system confirmed that representatives from managed care organizations, pharmacy benefit managers, hospitals, and Federal and State government agencies regularly request pharmacoeconomic information from manufacturers.[9] This information includes the data required for FDA approval, systematic reviews conducted by the academic community, "horizon scanning" programs that identify and evaluate data on emerging advances,[10] and, increasingly, data generated internally and externally via electronic datasets. However, the current process—relying on FDA's unsolicited requests guidance—impedes these entities from receiving the most up-to-date information about medical products. In addition, payors are increasingly seeking to enter into value-based contracts with manufacturers, further underscoring payors' need for HCEI.[11]

Payors also influence physician prescribing, both directly and through contracts with provider organizations that manage large populations. For example, patients today are twice as likely to be enrolled in insurance plans that incentivize providers to prescribe certain treatments

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[7] Draft Guidance, at Lines 48-49.

[8] 2016 Health Strategies Group Survey of Payors (*n=38*). The sample consisted of representation from 10 national managed care organizations ("MCOs"), 10 regional MCOs, 8 pharmacy benefit managers, and 10 large integrated delivery networks ("IDNs"). IDNs were required to have an active accountable care organization and a population health and or/risk program in place to participate in the survey [*hereinafter* 2016 Health Strategies Group].

[9] Analysis based on information collected through FormularyDecisions.com.

[10] "Horizon scanning" programs are intended to provide payors, providers, and other health care decision makers with information that will help them plan for introduction of important new tests and treatments. Some of these programs are operated by payors, commercial sector companies specializing in such information, and private health technology assessment organizations.

[11] Avalere Health, *Health Plans Are Interested in Tying Drug Payments to Patient Outcomes: Hepatitis C and Oncology Are Top Therapeutic Area Targets* (June 16, 2016).

via cancer treatment pathways compared to only two years ago.[12] These changes mean that prescribing decisions not only are being made by independent physicians in solo practice, but also can be heavily influenced by sophisticated payors. Therefore, it is imperative that payors and population health decision-makers receive the information needed to make informed decisions in developing payment models and designing utilization management for their patient populations.

B. Payors Require Up-To-Date Information About Investigational Products and Unapproved Uses of Approved Products

Payors also routinely seek information about investigational products *and* unapproved uses of approved products, particularly when such uses are being investigated for a potential label expansion. The Draft Guidance recognizes that payors "need to . . . plan for and make coverage and reimbursement decisions far in advance of" marketing."[13] As FDA notes, payors are also "interested in receiving information from firms about medical products that are still under investigation or review by FDA." These concerns apply with equal force to *both* investigational products *and* investigational uses of approved products. Payors have identical business planning needs for investigational products and investigational uses, and FDA should confirm that the same approach applies to communications in both contexts.

In a PhRMA survey of payors, nearly all entities surveyed—97%—responded that they would be interested in receiving additional information from manufacturers about the efficacy of products for unapproved uses, provided such information is scientifically- and statistically-sound, appropriately contextualized, and transparent about how it was developed.[14] Based on a separate survey of its member companies also conducted in connection with developing this comment letter, PhRMA learned of many instances in which payors would have wanted information about an investigational indication much earlier than the manufacturer was comfortable communicating the information. For example, in one instance, a medicine was originally approved for the adult population despite the fact that the disease being treated is most prevalent in children. At the time of FDA approval, the manufacturer was conducting a pediatric clinical trial and was not able to update the product labeling for 18 months after initial FDA approval. Because of the lack of clarity in FDA regulations and guidance, during that 18-month period, the manufacturer did not discuss the investigational pediatric indication with payors.

Payors have expressed a need for up-to-date information about investigational products and both approved and unapproved uses of approved products. While the Draft Guidance recognizes payors' need for this information, PhRMA is concerned the Draft Guidance does not adequately address the issue, particularly with respect to unapproved uses of approved products.

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[12] PhRMA analysis of EMD Serono, Specialty Digest: Managed Care Strategies for Specialty Pharmaceuticals, 12th Edition, http://www.specialtydigest.emdserono.com/Default.aspx.

[13] Draft Guidance, at Lines 56-59.

[14] 2016 Health Strategies Group Survey of Payors.

II. While Much of the Draft Guidance Reflects an Appropriate Balance, Some Important Changes and Clarifications Should Be Made in Final Guidance

When finalizing the Draft Guidance, PhRMA urges FDA to adopt the recommendations set forth in this comment letter, as well as the PhRMA-BIO Principles. A modified regulatory approach to payor communications, guided by the PhRMA-BIO Principles, will help to ensure that this sophisticated audience receives access to truthful, non-misleading health care economic information, without putting patients at risk.

In brief summary, Principle 1 states that manufacturers should communicate accurate information based on scientifically- and statistically-sound methodologies; Principle 2 emphasizes that FDA-approved labeling is a primary source of information for manufacturer communications with healthcare professionals; Principle 3 states that manufacturers should provide scientific substantiation with communications regarding information not contained in the FDA-approved labeling; Principle 4 notes that broader availability of information will help payors make informed decisions for their patients; Principle 5 directs that manufacturer communications should be tailored to the sophistication of the audience; Principle 6 emphasizes that the wealth of available science-based information can help improve healthcare decision-making; Principle 7 acknowledges that early communications with payors facilitates patient access to life-changing medicines; Principle 8 notes that providing payors with real-world evidence will facilitate understanding of patient outcomes and healthcare costs; and Principle 9 states that communicating timely and accurate information published in peer-reviewed journals serves important public health and policy goals.

PhRMA and BIO adopted each of these Principles in recognition of the sophistication level of the audience and payors' need to have early access to product information in order to make informed budgeting decisions. We appreciate that FDA has considered many of these concepts in developing its approach to implementing the amendments made by section 3037 of the Cures Act as set forth in the Draft Guidance; however, we are concerned about certain aspects of the approach which we feel are unduly burdensome and unnecessary to protect public health.

A. Appropriate Scope of Audience for Communication of HCEI

In Q. A.2./A. A.2. of the Draft Guidance, FDA proposes that the appropriate audiences to receive HCEI should include "payors, formulary committees[,] . . . drug information centers, technology assessment panels, pharmacy benefit managers, and other multidisciplinary entities that review scientific and technology assessments to make drug selection, formulary management, and/or coverage and reimbursement decisions on a population basis for health care organizations."[15] While PhRMA agrees with this definition, we encourage FDA to clarify that the audience also includes the individual members of the entity types included in the definition.

[15] Draft Guidance, at Lines 96-101 (footnotes omitted).

Additionally, the Draft Guidance asserts that it does not apply to "health care providers who are making individual patient prescribing decisions."[16] Because it is quite common for health care providers to serve on formulary committees, PhRMA requests that the Agency confirm that when a health care provider is serving in the capacity of a formulary decision-maker, the draft guidance does apply to that provider.[17]

PhRMA further recommends that FDA amend the scope of audience to account for audience members who may or may not engage in a "deliberative process." In particular, the Draft Guidance provides:

> Such entities are constituted to consider HCEI (and other types of information) through a "deliberative process" and should have the appropriate range of "knowledge and expertise in the area of health care economic analysis" needed to interpret HCEI presented to them to inform their population-based decision making process. Expertise in this area is essential to understand and evaluate health care economic analyses and their limitations.[18]

FDCA section 502(a) now encompasses payors, formulary committees, and other "similar" entities "with knowledge and expertise in the area of health care economic analysis" carrying out their "responsibility[y] for the selection of drugs for coverage or reimbursement."[19] We are concerned that there may be other payors "with knowledge and expertise in the area of health care economic analysis" that may be restricted by the Draft Guidance's assertion that appropriate audiences must be "constituted to consider HCEI (and other types of information) through a 'deliberative process'"[20] Such a "deliberative process" requirement does not appear in the statute. We recommend that it be removed from the final guidance.

B. "Relates To" Requirement

PhRMA generally agrees with FDA's views in Q. A.4./A. A.4. regarding the type of HCEI that "relates to an [approved] indication."[21] But we encourage FDA to broaden the scope of HCEI that "relates to" an approved indication in some respects beyond the examples in the Draft Guidance. Specifically, FDA should clarify that HCEI "relates to" an approved indication

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[16] Draft Guidance, at Line 111.

[17] To the extent FDA retains a "deliberative process" requirement, PhRMA notes that an individual acting in their capacity as a member of an entity (*e.g.*, formulary committee) still engages in a "deliberative process." The individual must engage with the entity in such a "deliberative process" before making any decision for the "selection of drugs for coverage or reimbursement."

[18] Draft Guidance, at Lines 103-08 (footnotes omitted).

[19] 21 U.S.C. § 352(a)(1).

[20] Draft Guidance, at Lines 103-04.

[21] Draft Guidance, at Lines 135-136 (alteration in original) (internal quotation marks omitted); Q. A.4. and A. A.4.

when it is based on data that includes information about approved and unapproved indications. FDCA section 502(a) provides that HCEI cannot "relate[] *only to* an [unapproved] indication;"[22] however, nothing in the statutory language or the legislative history suggests that the statutory definition of HCEI excludes information that relates to *both* approved and unapproved uses of a product.

FDA recognizes that HCEI communications can derive from RWE. However, the Draft Guidance does not appear to recognize that RWE studies *routinely* include patients using the product in a manner not entirely consistent with the FDA-approved labeling. This is a function of the realities of medical practice. For example, manufacturers regularly conduct analyses of data generated from patient registries to assess the economic impact of product use in actual practice. And payors find this information useful in making coverage and reimbursement decisions even if certain patients in the registry were using the product in a manner not entirely consistent with FDA-approved labeling. Indeed, payors often find this information even more important than data derived exclusively from use in the approved indication, as such data reflects the real-world practice of medicine.

As many HCEI communications will be derived from real-world data, where it is extremely burdensome to ensure *every* use is entirely consistent with the approved indication, clarification is necessary to facilitate HCEI communications consistent with FDAMA 114. The Draft Guidance should clarify that HCEI "relates to" an approved indication when it is based on data that includes information about approved and unapproved uses. In this regard, FDA should clarify that example 2 on page 8 of the Draft Guidance involves information derived from studies designed to address unapproved uses of a medical product.

C. "Competent and Reliable Scientific Evidence" Standard

PhRMA generally agrees with FDA's characterization in Q. A.5./A. A.5. of the evidentiary support that manufacturers should have for HCEI disseminated to payors. In particular, we agree that HCEI is supported by "competent and reliable scientific evidence" ("CARSE") if the information is "developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results," and that this standard should apply to both economic and non-economic components of, and assumptions underlying, the information manufacturers convey to payors and population health decision-makers.[23] We also agree that manufacturers should be able to rely "on good research practices for substantiation developed by authoritative bodies," including standards developed by the International Society for Pharmacoeconomics and Outcomes Research ("ISPOR") and the Patient-Centered Outcomes Research Institute ("PCORI").[24]

PhRMA understands that FDA's inclusive language listing ISPOR and PCORI as examples reflects the Agency's acknowledgement that there are also good research practices and

[22] 21 U.S.C. § 352(a)(2)(B) (emphasis added).

[23] Draft Guidance, at Lines 181-83.

[24] Draft Guidance, at Lines 186-89.

standards developed by other authoritative bodies. These authoritative bodies may include, without limitation, the Agency for Healthcare Research and Quality, the AMCP, the American Academy of Health-System Pharmacists, the International Society for Pharmacoepidemiology, and the International Society for Quality of Life Research, among others. Specific examples of practices and standards include, without limitation, the Good ReseArch for Comparative Effectiveness principles,[25] recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine,[26] and any other similar source of scientifically- and statistically-sound methodologies. Likewise, PhRMA assumes that FDA expects manufacturers to use discretion in resolving potential inconsistencies or conflicting expert opinions among scientific standards developed by these well-respected bodies.

PhRMA also agrees with FDA that real-world evidence can satisfy the CARSE level of substantiation. We suggest that FDA incorporate in final guidance the concepts and policy rationale enumerated in FDA's draft guidance entitled Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices – Draft Guidance for Industry and Food and Drug Administration Staff.[27] PhRMA supports FDA's use of the standards explained in that guidance as a basis for clarifying when real-world evidence is appropriate to communicate to payors and population health decision-makers.

D. Disclosures

PhRMA generally agrees with FDA in Q. A.7./A. A.7. that disclosures providing appropriate context are important to ensure that communications are truthful and non-misleading for their intended audience.[28] Indeed, providing such contextual information is consistent with PhRMA-BIO Principle 3, which states that "[t]o help ensure that [sophisticated audiences] can appropriately weigh data that are not contained in the FDA-approved labeling for a drug, companies should make appropriate disclosures."[29] However, the full slate of required disclosures in the Draft Guidance would recommend that manufacturers provide payors with disclosures that provide much more information than is necessary to ensure payors have appropriate context for the communicated information and suggests a level of paternalism inconsistent with First Amendment jurisprudence.

The disclosures proposed in the Draft Guidance would be both unnecessary and unreasonably burdensome in many instances, particularly if required to be presented repeatedly.

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[25] Nancy A. Dreyer et al., *The GRACE Checklist: A Validated Assessment Tool for High Quality Observational Studies of Comparative Effectiveness*, 22 J. MANAGED CARE & SPECIALTY PHARM. 1107 (Oct. 2016).

[26] COST-EFFECTIVENESS IN HEALTH AND MEDICINE (Peter J. Neumann, et al., eds., Oxford University Press 2d ed. 2016) New York: Oxford University Press, 2017. Print.

[27] FDA, Draft Guidance, Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices—Draft Guidance for Industry and Food and Drug Administration Staff (2016).

[28] *See generally* Draft Guidance, at Lines 211-356.

[29] PhRMA-BIO Principles, at Principle 3.

For example, rather than provide information that permits "payors to fully understand the HCEI,"[30] manufacturers should be permitted to provide sufficient context and disclosures so that the HCEI is truthful and non-misleading. Furthermore, it is unreasonable and unnecessary to require that each and every enumerated disclosure be included with each and every communication to a payor or population health decision-maker; such a requirement would result in significant redundancies in what is being communicated, in addition to being impractical from a presentation standpoint. Moreover, by repeating the same set of lengthy disclosures during every exchange of information, the effect of the disclosures may become less appreciable. Manufacturers should retain discretion to make reasoned and responsible determinations regarding which disclosures are appropriate for each communication. As sophisticated audiences, payors and population health decision-makers are fully capable of processing complex information, and would not need to receive every disclosure set forth in the Draft Guidance with every communication from a manufacturer regarding HCEI. Therefore, FDA should permit a manufacturer, for example, to refer a payor to information contained in a dossier rather than requiring the manufacturer repeatedly to communicate all relevant information.

Additionally, there are a few specific disclosures that PhRMA recommends FDA amend when finalizing this Draft Guidance. First, PhRMA recommends that FDA introduce flexibility into the proposed requirement that manufacturers disclose omitted studies.[31] It is overly burdensome to require manufacturers to disclose all such information during communications with payor audiences. With respect to the same proposed disclosure requirement, PhRMA also suggests revising the sentence to read as follows: "the presentation of HCEI would not be considered to be balanced and complete if ~~relevant~~ data or information *about a product necessary to understand and contextualize the communication* is available but was not considered and included in the analysis."[32] Manufacturers may collect and analyze data other than product data when analyzing HCEI in order to ensure that they have a complete picture (*e.g.*, the cost of one night in the hospital or the cost of a missed day of work). However, FDA should clarify that such other information, which does not relate specifically to use of the drug product, does not need to be included with product disclosures as a data source.

Second, FDA should permit manufacturers flexibility with respect to disclosing potential financial or affiliation biases, as such information regularly changes and the audience understands how to evaluate the merits of HCEI without such a disclosure requirement.[33]

Third, FDA should amend the disclosure regarding assumptions to permit manufacturers to provide "[a]ll evidence to support the assumption[] . . ." *upon request*.[34] Otherwise, this is a burdensome requirement for manufacturers and may also result in payors receiving unnecessary information.

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[30] Draft Guidance, at Line 216.

[31] Draft Guidance, at Lines 330-43.

[32] Draft Guidance, at Lines 330-33 (italicized text added).

[33] Draft Guidance, at Lines 351-56.

[34] Draft Guidance, at Lines 280-81.

Fourth, PhRMA requests that FDA confirm that manufacturers do not have a duty to update payors and population health decision-makers with changes to HCEI. Payors are a highly sophisticated audience fully capable of evaluating information they receive from manufacturers and tracking any changes to such information on their own. As such, requiring manufacturers to provide updates to payors for changes or developments would be unduly burdensome. If FDA does believe such a duty exists, PhRMA requests that updates be limited to instances in which previously communicated HCEI has been rendered false or misleading in light of new information.

E. Comparative HCEI

FDCA section 502(a) defines HCEI to include analyses "comparative to the use of another drug, to another health care intervention, or to no intervention."[35] While FDA acknowledges this definition in the Draft Guidance in Q. A.1./A. A.1.,[36] the only example FDA offers of a permissible comparison involves "analyses . . . derived from studies comparing the safety or effectiveness of a drug for its approved indication to another drug or intervention or to no treatment."[37] Although this example may suggest that a proper comparison derives from head-to-head data, FDCA section 502(a) contains no such requirement. FDA recognizes this when it confirms that manufacturers may provide comparative HCEI "in the absence of data from head-to-head controlled clinical trials."[38] Therefore, we ask that FDA explicitly confirm in final guidance that HCEI may be based on comparisons that do not derive from head-to-head studies, as required by the statute.

F. Investigational Products

PhRMA requests additional clarity regarding FDA's proposed approach in Q. B.1./A. B.1. for information that may be communicated to payors about investigational products.[39] For one, FDA should clarify that the appropriate scope of the audience for the communication of HCEI about investigational products broadly includes payors, formulary committees, and other population health decision-makers, as described in Q.2.A.2. Additionally, we seek assurance that FDA will not object under 21 C.F.R. § 312.7(a) or otherwise to communications to such payors and population health decision-makers regarding investigational products when the communications do not include all of the disclosures that FDA requires manufacturers to include with communications regarding approved indications. In addition to stating clearly that FDA will exercise enforcement discretion with respect to § 312.7(a)—deeming communications that comport with the approach set forth in the Draft Guidance as compliant—the Agency ultimately should update its regulations to implement its final guidance.

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[35] 21 U.S.C. § 352(a)(2)(A).

[36] Draft Guidance, at Lines 75-77.

[37] Draft Guidance, chart at Line 149.

[38] Draft Guidance, at Lines 189-93.

[39] Draft Guidance, at Lines 413-77.

FDA also must confirm that its approach to investigational products likewise applies to unapproved uses of FDA-approved products that are under investigation. PhRMA believes that there is no relevant distinction between communications regarding an investigational drug, as defined in footnote 7 of the Draft Guidance, and communications about products that have already been approved by FDA for at least one indication but are under investigation for an unapproved use. Implementing a regulatory structure that distinguishes between investigational products and unapproved uses of approved products undermines the benefit that payors, and therefore patients, receive from broader communication channels between manufacturers and payors. As discussed above, payors are interested in receiving information about drugs well in advance of the drug being marketed for any particular use. They want to be informed about both new products and new uses of approved products to be able to make fully-informed coverage and reimbursement decisions for patients. Manufacturers should be able to share the same information about investigational products and unapproved uses of approved products so long as the communications meet the standards set forth in the Draft Guidance. Therefore, FDA should confirm that the Draft Guidance applies not only to entirely investigational products, but also to unapproved uses of FDA-approved products.

With respect to unapproved uses of approved products, simply referring manufacturers to the unsolicited requests and good reprint draft guidance is overly restrictive.[40] For the reasons set forth in our comments being simultaneously filed 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 Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products memorandum,[41] FDA's restrictions on truthful and non-misleading communications about unapproved uses are inconsistent with modern First Amendment jurisprudence and do not reflect an appropriate balance of the competing interests at stake. We refer FDA to our separate comment letter for further discussion regarding the appropriate balance between First Amendment interests and the FDA's interests in protecting the public health and maintaining the integrity of the FDA approval process.

PhRMA also suggests that FDA amend the proposed requirements in Q. B.2./A. B.2. for contextual information that manufacturers would be required to provide along with communications regarding investigational products or unapproved uses of FDA-approved products. Specifically, PhRMA believes that FDA's suggestion that manufacturers "provide follow-up information to payors if previously communicated information becomes outdated as a result of significant changes or as a result of new information regarding the product" is overly burdensome.[42] It is unclear what FDA would consider to be a "significant change." In addition, the other transparency requirements in place are sufficient to protect patient health, and FDA

[40] *See* Draft Guidance, at Lines 393-402 & nn.51-53.

[41] Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, 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).

[42] Draft Guidance, at Lines 465-70.

should not place such an administrative burden on manufacturers given the highly sophisticated nature of the payor audiences involved.

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PhRMA appreciates the opportunity to comment on this Draft Guidance document and looks forward to continued collaboration with the FDA on the Agency's approach to communications with payors and other population health decision-makers. We value our relationship with the Agency and would be pleased to discuss these comments further.

Respectfully submitted,

/s/	/s/	/s/
James C. Stansel Executive Vice President & General Counsel	Lori Reilly Executive Vice President, Policy & Research	William Chin, M.D. Executive Vice President, Science & Regulatory Advocacy