

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.