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LIFE SCIENCES

WITH A WHISPER, NOT A SHOUT, FDA BREAKS SILENCE ON MEDICAL PRODUCT COMMUNICATIONS

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By releasing two draft guidances on medical product communications on January 18, FDA has broken its long silence on medical product communications. The timing of the release in the waning days of the Obama administration appears to be an effort by FDA to get its position on the record in an attempt to avoid being trumped by the incoming administration; that effort may be thwarted by the current administration's move to roll back recently issued regulations.

One draft guidance addresses drug and device manufacturer communications with payors, formulary committees, and similar entities and provides direct and substantial recommendations of the kind that manufacturers have been requesting for years.[1] The other draft guidance covers medical product communications that present information that is "consistent with the FDA-required labeling" for the product, but that is not contained in such labeling.[2] It seems to do little more than summarize the standard approach of industry and FDA to promotional material.

The draft guidances were released on the same day that FDA extended by 90 days[3] the comment period relating to "Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products," which was set to end on January 9, 2017. While the draft guidances are welcome, industry is much more interested in seeing FDA articulate a policy on unapproved uses of approved or cleared products, and indeed has been requesting such a policy for many years.

Draft Guidance on Communications with Payors, Formulary Committees, and Similar Entities

The first FDA draft guidance covers drug and device companies' communications with payors, formulary committees, and similar entities. Written in a question-and-answer format, it provides reasonably clear and detailed information about what communication FDA considers acceptable. Broken into two main sections, it addresses communication of health care economic information (HCEI) about approved drugs, and communication of factual information about unapproved drugs.

Section 502(a) of the Federal Food, Drug, and Cosmetic Act defines HCEI as "any analysis … that identifies, measures or describes the economic consequences … of the use of a drug."[4] The draft guidance notes that HCEI may be presented in a number of formats, including evidence dossiers, reprints from peer-reviewed journals, and software. The guidance also specifies that HCEI can be provided only to certain audiences with knowledge and expertise in the area of health care economic analysis, such as payors, formulary committees, drug information centers, technology assessment panels, and pharmacy benefit managers for health care organizations. The guidance does not allow dissemination of HCEI to doctors making individual patient prescribing decisions.

Most significantly, the guidance establishes two key principles: HCEI must "relate to an approved indication" and must be based on "competent and reliable scientific evidence" (CARSE).[5]

Related to an Approved Indication

FDA lists ten examples of HCEI analyses that could be considered "related to an approved indication," including analyses of dosing, patient subgroups, length of hospital stays, surrogate endpoints, clinical outcome assessments, practice settings, burden of illness, persistence, comparisons, and duration of use.

On the other hand, FDA provides two examples of HCEI analyses that would not be considered to be related to an approved indication – an analysis of disease course modification for a drug approved only to treat symptoms of a disease and HCEI analyses derived from studies in patient populations that are not within the indicated patient population.

Competent and Reliable Scientific Evidence (CARSE)

Regarding what CARSE is, the guidance says that HCEI should be developed using generally accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable

results. In this area, FDA may defer to external authoritative bodies, such as the International Society for Pharmacoeconomic and Outcomes Research and the Patient-Centered Outcomes Research Institute. FDA intends to apply its CARSE standard to all components of HCEI, including inputs and assumptions related to economic consequences, not just clinical outcomes.

Information to Be Included When Disseminating HCEI

The draft guidance calls for manufacturers to include background and contextual information that will allow recipients to fully understand HCEI. This information includes the study design and methodology, the type of modeling technique, details about the patient population, the viewpoint of the economic analysis, the choice of comparator treatment, the choice of time horizon, the outcome measures, cost estimates, and a comprehensive listing of all assumptions and associated rationales. FDA also advises firms to disclose factors that may limit the generalizability of the economic analysis.[6]

If HCEI includes material differences from the FDA-approved labeling, it must present a conspicuous and prominent statement describing such differences.

Investigational Drugs and Devices

The draft guidance explicitly allows drug and device firms to provide payors with information about products prior to approval without running afoul of the FDA regulations prohibiting promotion of investigational drugs and devices (21 C.F.R. §§ 312.7(a) and 812.7(a)), provided that certain conditions are met. Notably, this permissive distribution of information extends only to communications about investigational products[7] and not to communications about unapproved or uncleared uses of approved or cleared products. The information provided must be unbiased, factual, accurate, and non-misleading. It can include product information such as device design, the indication sought, results from clinical or preclinical studies, the anticipated date of FDA approval/clearance, product pricing information, patient support programs, and marketing strategies.

The communication must be presented with (1) a clear statement that the product is under investigation and that the safety or effectiveness of the product has not been established and (2) information related to the stage of product development. The draft guidance also states that firms should provide follow-up information to payors if previously communicated information becomes outdated as a result of new information regarding the product or its review status.

Draft Guidance on Medical Product Communications that are Consistent with the FDA Required Labeling

The second new draft guidance provides recommendations for conveying information that is "consistent with the FDA-required labeling" in a truthful and non-misleading manner. This guidance serves as a "how-to" guide for manufacturer promotional review committees rather than illustrating any greater latitude under or loosening of current laws and regulations. However, there is a significant easing that can be gleaned from the guidance – FDA will permit one adequate and well-controlled study to substantiate promotional claims that are "consistent with the FDA-required labeling." In giving an example of a permissible comparative product claim, FDA states that such a claim may be based on a "head-to-head **study** indicating that [a] drug that is approved to treat high blood pressure in adults has superior efficacy to another drug that is also approved to treat high blood pressure in adults" (emphasis added).

FDA states that it will use a three-factor test to determine whether a communication is consistent with the labeling.

- **Factor 1:** Does the communication make representations or suggestions that differ from the product's labeled (1) indication, (2) patient population, (3) use limitations or directions for handling, preparing, or use, or (4) dosage or use regimen, route of administration, or strength?
- **Factor 2:** Do the representations/suggestions in the communication increase potential harm to health, relative to the information reflected in FDA labeling? (For example, altering the benefit-risk profile of a product.)
- **Factor 3:** Do directions for use in the FDA-required labeling enable the product to be safely and effectively used under the conditions represented/suggested in the communication?

If the answer to Factors 1 or 2 is yes or the answer to Factor 3 is no, FDA will not consider the communication to be consistent with the FDA-required labeling.

The draft guidance provides numerous examples of the kinds of information that could be consistent with the FDA-required labeling:

- Safety or efficacy comparisons of a medical product for its approved/cleared indication to another medical product approved/cleared for the same indication

- Additional context about the adverse reactions associated with the approved/cleared uses of the product
- The onset of action of the product for its approved/cleared indication
- The long-term safety and/or efficacy of products that are approved/cleared for chronic use
- The effects or uses of a product in specific patient subgroups
- Patient-reported outcomes
- Product convenience
- The mechanism of action

Similarly, the draft guidance also provides examples of the kinds of information that are not considered consistent with the FDA-required labeling for a product:

- The use of a product to treat or diagnose a different disease or condition than the product is approved/cleared to treat or diagnose
- The use of a product to treat or diagnose patients who are not included in the product's approved/cleared patient population
- The use of a product to treat a different stage, severity, or manifestation of a disease than the product is approved/cleared to treat
- The use of a product as monotherapy when it is only approved/cleared for use in conjunction with one or more other products or therapeutic modalities
- The use of a product through a different route of administration or in a different tissue type than the product is approved/cleared for
- The use of a different strength, dosage, or use regimen than the approved/cleared strength, dosage, or use regimen
- The use of a product in a different dosage form

Evidentiary Support

FDA states that communications that lack appropriate evidentiary support are likely to be false or misleading and can cause patient harm. Therefore, representations made by firms must be grounded in fact and science and presented with appropriate context. Firms should ensure that any data, studies, or analyses relied upon are scientifically appropriate and statistically sound. This evidence should be accurately characterized in the communication, including limitations of the strength of the evidence and the conclusions that can be drawn from it.

FDA recommends that study results and other data and information be accurately represented in the communications (i.e., material aspects of study design, methodology, and material limitations should be clearly and prominently disclosed). Further, the communication should accurately characterize and contextualize the relevant information about the product, including by disclosing unfavorable or inconsistent findings. FDA also advises that, before disseminating a communication regarding a medical product, firms should have qualified medical, legal, and regulatory personnel carefully review the communication to ensure it is not false or misleading.

Conclusion

Comments on both draft guidances are due within 60 days of publication. While these guidances are welcome, FDA has, as mentioned above, failed to clarify its position on off-label communications for approved and cleared products. Instead, the agency reopened the comment period on its docket for "Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products" for an additional 90 days and released a 63-page memorandum on its views on the First Amendment issues related to off-label communications[8]. Although too long to summarize in this alert, life sciences companies must be aware that the majority of this memorandum consists of FDA consideration and rejection of a dozen possible approaches to FDA regulation of off-label promotion.

Pharmaceutical and medical device manufacturers should proceed cautiously while awaiting more definitive regulations. It is important to consult with counsel for assistance in navigating this challenging landscape prior to engaging in communications that may implicate an enforcement action for false or misleading communication.

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[1] FDA, Guidance for Industry and Review Staff: "Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers" January 18, 2017, available here.

[2] FDA, Guidance for Industry: "Medical Product Communications That Are Consistent With the FDA-Required Labeling – Questions and Answers" January 18, 2017, available here.

[3] Federal Register, January 19, 2017, available at https://federalregister.gov/d/2017-01013.

[4] 21 U.S.C. 352(a), as amended by Section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and Section 3037 of the 21st Century Cures Act.

[5] Id.

[6] 21 CFR 314.81(b)(3)(i).

[7] As used in this guidance, the term "investigational products" refers to drugs and devices that are not yet approved/cleared by FDA for any use (but which must be approved/cleared to be legally marketed), including products for which firms have submitted or plan to submit a new drug application (NDA), a biologics license, application (BLA) (including an application submitted under the 351(k). pathway), an abbreviated new drug application (ANDA), a premarket approval application (PMA), a 510(k) submission, a de novo submission under section 513(f)(2) of the FD&C Act (21 U.S.C. 360c(f)(2)), or a Humanitarian Device Exemption (HDE) application.

[8] FDA, Memorandum, Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products, January 2017, available at https://www.regulations.gov/document?D=FDA-2016-N-1149-0040.

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