FDA Got An Earful: FDA's Part 15 Public Hearing on Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products

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Last week, FDA held a much-anticipated Part 15 public hearing seeking commentary on its regulation of speech about unapproved uses of approved products. As the agency noted in its Federal Register announcement, the meeting sought input on a range of issues, including how increased communications about unapproved uses could impact public health, and whether the impact would differ across different categories of medical products; factors manufacturers consider when making decisions about providing information on unapproved uses; standards that should apply to unapproved use communications to minimize the potential for these communications to be misleading; how FDA could monitor manufacturers' communications about unapproved uses; and what types of regulatory and policy changes may be appropriate to provide greater certainty and clarity to regulated industry.[1]

Over two full days (November 9-10, 2016), the agency heard presentations from more than 60 speakers representing medical product manufacturers, payors, providers, and patients.[2] Consumer advocates, the media, and academic researchers also shared their perspectives with an FDA panel that included Commissioner Robert Califf, Deputy Commissioner Rachel Sherman, Associate Commissioner for Policy Leslie Kux, Senior Policy Advisor Kristin Davis, Senior Counsel Karen Schifter, OPDP Director Tom Abrams, CBER Associate Director of Policy Diane Maloney, and CDRH Deputy Director of Policy Lauren Silvis.

Commissioner Califf's opening remarks acknowledged that the agency is undertaking a comprehensive review of its policies; however, the agency clearly remains concerned about potential public safety implications of broader communication about unapproved uses, as well as the potential impact on incentives for product sponsors to seek supplemental approvals and for patients to participate in clinical trials. Although the Commissioner and other agency officials stopped short of articulating specific policy or regulatory proposals during the hearing, the FDA panel's questions posed to certain presenters suggested a particular focus on the following:

- What types of distinctions can be drawn between communications about an unapproved use versus those about information that is not in the labeling but relates to an approved use;
- How manufacturers determine the types of evidence and information on an unapproved use that can be presented in a truthful and non-misleading manner; and

- The role of the peer-review publication process in determining the types of evidence and information that might be appropriate for communication about unapproved uses.

Several presenters stated that they plan to submit further comments to the docket to address, among other things, questions that were asked by agency officials at the hearing. As a result, it may be informative to monitor the public meeting docket (FDA-2016-N-1149) over the coming weeks. The docket will be open until January 9, 2017.

The breadth of perspectives presented at the public meeting and the agency's active questioning of presenters foreshadow the likelihood of continued, vigorous discussion and debate. It also remains to be seen what impact the change in presidential administration may have on the agency's next steps in this complex area.

Brief Summaries of Stakeholder Perspectives

Below are high-level summaries of key themes expressed by stakeholder groups that were represented at the public meeting. These high-level summaries do not reflect the numerous nuances and situation-specific considerations that individual speakers presented to the agency. These more detailed aspects of the presentations will be available when FDA posts a recording and full transcript of the public hearing on its website.

Manufacturers

In general, medical product manufacturers underscored that allowing a greater degree of truthful and non-misleading communication about unapproved uses will enhance patient care by providing health care providers (HCPs) and payors with timely and clinically relevant information to make treatment and reimbursement decisions. Several companies pointed out that for some diseases and patient populations, unapproved uses are the standard of care, making communications about these uses particularly important. Manufacturers also emphasized that current FDA policy places, in their view, unconstitutional burdens on truthful, non-misleading commercial speech, and they noted that the industry is not seeking free rein to communicate information on unapproved uses. Rather, regulated industry is asking that the agency articulate clearer policies that will allow responsible, truthful and non-misleading promotional communication about information that is not included in FDA-approved labeling. Indeed, many manufacturers focused their comments on communications to HCPs and payors—two groups that are well-equipped to critically assess truthful and non-misleading communications about unapproved uses of products—as opposed to direct communications with patients.

The FDA panel asked industry speakers numerous questions, including what standards should be used to assess the quality of scientific information on unapproved uses, how manufacturers determine whether a communication is non-misleading, and what incentives manufacturers would have to conduct rigorous, well-controlled clinical trials if they are able to communicate about unapproved uses based on other types of data. Some speakers noted that FDA-approved labeling will always have an important role as the primary source of information about a medical product, and that payors' and HCPs' demands for rigorous, high-quality data, as well as product liability considerations, will continue to motivate manufacturers to conduct well-controlled trials and seek FDA approvals for expanded indications. Several manufacturers stated that they plan to submit comments to the docket in response to the agency's questions, including insights on how they have handled situations where they decided to pursue promotional communications regarding information falling outside a product's FDA-approved labeling.

Some speakers highlighted considerations that are unique to certain classes of products. For example, the American Association of Tissue Banks noted the need for clarification of FDA's policy toward manufacturer communications regarding human cells, tissues, and tissue-based products (HCT/Ps) because section 361 HCT/Ps have no FDA-approved labeling and their status is based, in part, on the agency's views of a manufacturer's objective intent. In addition, medical device manufacturers and trade groups emphasized that the agency should not adopt a "one size fits all" policy because there are important differences between industries. For devices in particular, they explained that randomized controlled trials are often not practical, so other evidence, such as retrospective data and data from

product registries or observational studies, should be recognized. Also, because many devices undergo iteration changes at a faster pace than drugs and can be cleared more quickly than drugs are approved, and because devices are often complex and used in high-risk procedures, timely release of safety data and other information is critical for training and supporting HCPs who are using those devices. Restricting discussion to the cleared/approved labeling ignores the additional knowledge gathered throughout clinical use that can help advance medical care and protect patients.

Payors

Payors noted that they need to assess the clinical benefits and overall value of new medical products well in advance of FDA approval or clearance, in order to make timely and accurate decisions about coverage and reimbursement. Specifically, payors expressed the desire to receive early information about manufacturers' product pipelines and plans for additional indications for an already approved product. Payors also noted that good quality real-world data would allow payors to make value assessments based on information that may be more representative than the results of randomized controlled trials. Echoing manufacturers' comments, payors stated that FDA's current policies prevent open discussion of this information and data because manufacturers are wary of potential enforcement risk, and urged the agency to establish broader and more clearly delineated guidance for industry. For example, the Academy of Managed Care Pharmacy (AMCP) suggested a safe harbor for manufacturer communications regarding clinical information for new molecules and expanded indications within 12-18 months prior to approval. The Pharmaceutical Care Management Association asked FDA to consider a compendium-style database that would provide comprehensive information regarding medical products, rather than just manufacturer-selected data.

Providers

Two professional societies spoke at the meeting in support of communication of scientifically-valid information regarding unapproved uses. Because physicians have a duty to obtain the best outcomes for their patients, actual use of medical products often can extend beyond their approved or cleared indications. The American Association of Neurological Surgeons also explained that because randomized controlled trials are impractical for some products (e.g., spinal surgery products), real world data is necessary to fill evidence gaps. FDA asked whether physicians actually use FDA-approved labeling and whether physicians are equipped to assess data from studies other than randomized controlled trials of on-label uses. The physician groups responded that residents are trained to put this type of information in context for risk-benefit assessments, and that additional data and information are needed to improve patient outcomes and find new cures.

Patient and Consumer Groups

Patient and consumer groups presented conflicting views on whether patients and physicians prefer greater communication regarding unapproved uses. Groups such as Public Citizen and the Consumer Union Safe Patient Project offered data showing that off-label use of medical products leads to overuse and more adverse events. They asserted that patients cannot provide "informed consent" to an unapproved use because product labeling does not include information about risks and benefits associated with that use. These groups emphasized FDA's role in policing the science that is disseminated to the public, and predicted that more permissive communication about unapproved uses would undermine sponsors' incentives to invest in high-quality clinical research required for FDA approval.

With respect to medical devices in particular, concerns were raised about unapproved uses of products that are cleared based on a finding of substantial equivalence to a predicate device, and whether communications about unapproved uses for cleared devices can ever really be truthful and non-misleading. Citing the recent Vascular Solutions case as an example, one presenter noted that the medical device industry tends to gain initial clearance of a device without clinical testing, develops a new iteration of the device without seeking clearance for those changes under a regulatory

loophole, and then promotes expanded uses that lack adequate scientific support. Some speakers called for transparency and specific data collection regarding how many injuries and deaths result from unapproved uses of devices and drugs.

In contrast, patient groups for diseases with few or no approved treatments, such as lupus, pediatric cancers, and mental illnesses, urged freer flow of information about unapproved uses, including data from studies other than randomized controlled trials. These groups pointed out that unapproved uses of an approved product are often the standard of care for such diseases, and manufacturers have the most comprehensive safety information about these uses. Limiting discussion of data and information about these uses, they suggested, will lead to lack of information and exacerbate potential safety issues. They asserted that these data also can be essential to help patients obtain reimbursement for these uses.

Other Stakeholders

The Washington Legal Foundation (WLF) argued that FDA's "adequate and well controlled" standard for approval should not be the standard for falsity, and that the standard for what is misleading should take the intended audience into account. One professor proposed, in response to FDA questions about how manufacturers should handle later data that calls into question previous data regarding an unapproved use, that FDA could publicly release what it believes to be current information.

Critics of greater communication regarding unapproved uses questioned the effectiveness of disclaimers, argued that existing safe harbors are sufficient, and highlighted concerns about direct-to-consumer promotion about unapproved uses. Dr. Joshua Sharfstein, former Principal Deputy Commission of FDA, noted that the agency was created specifically to prevent unsubstantiated claims about medical products.

Carlo Felizardo also contributed to this report.

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