The Beat Goes On: FDA Continues to Maintain its Position on Off-Label Promotion Policy

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The Food and Drug Administration recently reopened its docket for submission of written comments following its November 2016 public hearing, which addressed how to best align public health interests served by FDA's regulatory approach related to company communications regarding unapproved uses, i.e., off-label promotion, of medical products with recent developments in science, technology, and the law. (We have discussed the public hearing in an AGG webinar.) In addition, the agency placed a Memorandum, "Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products," in the docket to provide additional background as it re-examines its off-label promotion policy.

Taking a page from Sonny and Cher, to FDA, the beat goes on. The agency maintains its enforcement position on, and concerns about, off-label promotion. However, it keeps open the door to a potential compromise by reopening the comment period for the aforementioned docket until April 19, 2017. This Bulletin highlights the contents of the Memorandum. It provides a window into FDA's current thinking and where it might go. We will not discuss the larger issue of FDA's challenges with off-label promotion and the current regulatory framework, as we have done so in previous Bulletins.

Past Court Cases

In its Memorandum, FDA noted the limitations of the 2nd Circuit decision in *U.S. v. Caronia*.[1]

- FDA concluded that application of the court's decision is limited to only a specific construction of the Federal Food Drug, and Cosmetic Act's misbranding provisions, rather than an evaluation of FDA's current approach to marketing of unapproved uses of medical products
- FDA said that the decision failed to consider multiple components of the public health interests advanced by the agency's current approach
- FDA noted that the 2012 decision was issued prior to the release of a Canadian study showing a correlation between unapproved uses and adverse drug events

FDA rejected the analysis described by some commenters that the current restrictions on off-label promotion are content-and speaker-based and, therefore, subject to heightened scrutiny under *Sorell v. IMS Health Inc.*, a 2011 U.S. Supreme Court decision.

- FDA relied on the *Sorrell* decision for its position that "content-based restrictions on protected expression are sometimes permissible, and that principle applies to commercial speech"
- FDA also argued that, even if the restrictions are categorized as content- and speaker-based, courts have recognized that they are appropriate under the circumstances for which FDA applies the restrictions

1 We have discussed the Caronia case in a previous publication: http://www.agg.com/files/uploads/Client-Alerts/Kitchens-Minsk-Second-Circuit-Rules-Off-Label-Promotion-is-Protected-Speech.pdf.

FDA believes that its current regulatory framework for off-label promotion advances a number of public health interests:

- motivating the development of scientific data on safety and efficacy; preventing harm to members of the public; protecting against fraud, misrepresentation and bias; preventing the diversion of limited health care resources; ensuring required labeling is accurate and informative; protecting the integrity and reliability of promotional information regarding the uses of medical products; protecting human subjects receiving experimental treatments; ensuring informed consent; and maintaining incentives for clinical trial participation and innovation

FDA concedes that off-label promotions may advance other public health interests:

- for some patients, approved therapies are not available and unapproved uses could offer the only treatment option
- reliable scientific information regarding unapproved uses may help further scientific research, for example, through hypothesis generation
- information about unapproved uses may encourage the collection of outcomes on those uses and help identify those that present a greater risk of harm to patients

Alternative Approaches

In its Memorandum and November 2016 public hearing, FDA provided feedback on some alternative approaches advanced by commenters, and seeks further public comment on proposed alternatives, as well as to continue the discussion of how any currently proposed alternatives would advance the public health. The following is a brief summary of the proposed alternative approaches and FDA's comments and responses.

Prohibiting altogether the use and/or prescribing of an approved/cleared medical product for an unapproved new use.

- This approach would promote scientifically robust research into unapproved uses, but it fails to consider the public health interests in allowing providers to determine best treatments for patients in specific circumstances.

Barring approval of generics and other affected products until all periods of exclusivity on the reference product have expired.

- This approach would be contrary to the goals of Congress, which sought to ensure that brand name manufacturers would have patent protection and marketing exclusivity to incentivize development and enable the recovery of their investments in developing new drugs, while also ensuring the rapid availability of lower-priced versions of the drug once applicable patent protection and exclusivity expired.

Creating ceilings or caps on the number of prescriptions for an unapproved use.

- This approach is problematic because, once operative, the cap would limit provider discretion in determining treatments for patients.
    - further, before the cap is reached, firms could encourage the use of a product for an unapproved use with none of the safeguards of FDA review
    - it is also unclear how the cap would be determined and if it could be determined in a non-arbitrary way

Limiting Medicare and Medicaid reimbursement to approved uses.

- This approach would limit provider discretion and result in health disparities through the elimination of the prescribing of unapproved uses for Medicare and Medicaid patients, while continuing them for non-Medicare and non-Medicaid patients.

Prohibiting specific unapproved uses that are exceptionally concerning or developing tiers based on level of safety concerns with greater regulatory controls for higher risk products.

- This system would be inadequate to protect the public safety, because it would necessarily require a safety assessment depending on the generation of data regarding product dangers before any controls can be applied.
- With respect to lower risk products, this approach would undermine incentives to engage in prior approval review and to conduct the necessary research to demonstrate safety and effectiveness.

Requiring firms to list all potential indications for a product in the initial premarket application.

- This approach is problematic, because it is impossible to determine all potential uses of a medical product from an initial study.
- This approach would undermine government interests to incentivize robust research by firms, the requirements for pre-market safety and effectiveness review for each use, and the development of appropriate instructions for use.
- Initial applications could be significantly delayed if firms are required to obtain approval of all intended uses with an initial application.

Allowing firms to actively promote an unapproved use as long as they disclose that the use is unapproved and include other appropriate warnings.

- This approach is difficult, because it is unclear whether disclosures would be sufficient to prevent consumer harm and deceptions.
    - while warnings may help provide information necessary to assist in understanding data, studies have shown there are limitations to disclosures in terms of the recipient's perception and understanding

Educating health care providers and patients to differentiate false and misleading promotion from truthful and non-misleading information.

- This is an unrealistic approach, because such a program would be difficult to conduct on the scale necessary to combat the adverse effect of the various ways promotion can be false or misleading.
- Even if feasible, this approach would remove the burden from the manufacturer to ensure the safety and effectiveness of its products and place it on healthcare providers.

Reminding health care providers of potential malpractice liability.

- This approach does not advance the interest behind allowing providers to determine the best treatment option for patients, such as providing treatment options for which there are no approved treatments.
- Companies could bypass the prior approval process.

Taxing firms more heavily for sales of products for unapproved uses than for approved uses.

- This alternative does not align with governmental interests, at least in part, because it would affect all prescribing/uses of medical products for an unapproved use equally, despite whether there are circumstances warranting prescribing and use.
- This approach would allow companies to substitute a tax payment for the expense of conducting the scientific research needed to prevent harm to the public.
- It is unclear how such a tax would change company behavior or prevent, remedy or deter public health harms that prior review is designed to prevent.

Permit promotion of unapproved uses listed in medical compendia.

- This approach is problematic, because compendia rely on medical literature, so their decisions are not based on the same types of data and information that FDA relies upon in doing its review.
- This approach implicates the problem of publication bias, where trials with unfavorable results often go unpublished.
- There is the potential for firms to improperly influence compendia listings.

Limiting evidence that could be considered relevant to intended use to speech that the government can prove is false or misleading.

- This alternative is difficult, because firms could potentially promote unapproved uses of approved medical products based on incomplete data until the government can establish, after the fact, that the communication was misleading.
    - in the interim, patients could be harmed while FDA takes the time to prove the claim is wrong
- Incentives for generating scientific evidence would be undermined because, once a company has positive preliminary results, it would be unlikely to perform additional testing to generate more reliable evidence of safety and effectiveness.

AGG Observations

- With a triple aim to prevent patient harm, fraud, and waste of health care resources, it is unlikely that FDA will propose the elimination of prior approval, at least in some form, for unapproved uses of approved medical products.
- FDA has not backed off its position, but reiterates its legal argument, that it serves an important role in regulating off-label promotion. However, it recognizes the counterarguments and benefits of finding some compromise that relaxes, to some extent (not yet known), its enforcement policy.
- It is more likely that FDA will continue its robust regulation of such communications, notwithstanding the potential benefits that come with allowing promotion of unapproved uses of approved medical products.

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