Drug Companies Worry About New “Totality of Evidence” Standard

Is It an About–Face From the FDA on Off-Label Promotion?

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Incoming Food and Drug Administration (FDA) Commissioner Scott Gottlieb is a known proponent of allowing drug and device companies greater leeway to make the case for off-label use of their products. But Gottlieb faces a new controversy on that issue prompted by a final rule issued by the FDA in the waning days of the Obama administration.

The Pharmaceutical Research and Manufacturers of America (PhRMA) and other groups are incensed with the FDA over one section in that final rule that not only seemed to come out of left field, but appears to reverse a position the agency took a few years earlier. The new position expands a company’s liability for off-label promotion by deleting a sentence in a 1952 regulation that limited that liability. Moreover, the FDA replaced that 65-year-old sentence with a new one that drug manufacturers believe puts them more clearly in the agency’s enforcement sights.

The issue is essentially whether a manufacturer knows when it sells a drug that it is likely to be used off-label. The 1952 rule said that if a manufacturer had “knowledge” of off-label use it had to provide adequate labeling that is in accord with such intended uses. Of course, putting an off-label use on the label of an approved drug almost guarantees the FDA will take public comment on the drug almost guaranteed the FDA will take public comment on the drug for its approved use unless it filed a supplemental new drug application for the unapproved use. In a less extreme case, a company might refrain from putting adverse effects information on the label of a drug being used off-label. That was at the crux of a lawsuit Allergan filed against the FDA in 2009 in which the company argued it feared putting information on the label of Botox (onabotulinumtoxin A) related to potential dangers of using the drug off-label for spasticity. The sentence in the 1952 rule reads:

But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug or device introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.

In the Allergan case, the company had knowledge that Botox was going to be used off-label and wanted to give physicians some guidance on potential adverse effects when Botox was prescribed for spasticity. In its lawsuit, Allergan alleged that the FDA’s intended-use regulations from 1952 had chilled speech regarding methods to minimize the risks and improve the quality of patient care related to a particular off-label use. That case was settled, with the FDA stating “not all speech or actions by a manufacturer regarding an unapproved use is taken by FDA to be evidence of intended use.” The FDA further stated that, contrary to the last sentence of the 1952 rule, the agency “usually” does not rely on a manufacturer’s knowledge to infer an intended use.

In September 2015, the FDA proposed a rule that seemed to codify its position on intended use on intended use to comply with its assertions in the Allergan case. It proposed to delete that last sentence in the 1952 rule related to a manufacturer’s knowledge of off-label use.

Then came the 2017 final rule modifying the FDA’s 2015 position tucked into a regulatory proceeding entitled Clarification of When Products Made or Derived from Tobacco are Regulated as Drugs, Devices, or Combination Products; Amendments to Regulations Regarding “Intended Uses.” Rather than delete the final sentence of the 1952 intended-use definition as the agency proposed in 2015, the agency replaced it with an entirely new sentence that created an open-ended “totality of the evidence” standard. The “additional clarity,” as the agency calls it, expands on what the FDA argues has always been the case: that even if the manufacturer has no “direct knowledge” that a product is being used off-label, the agency can look to “circumstantial evidence” as part of the “totality of evidence” that the manufacturer “objectively intends” for the drug be used off-label.

The FDA appears to argue that the new totality of evidence standard gives manufacturers more protection than the 1952 sentence. According to the agency: The amended language no longer suggests that a manufacturer’s mere knowledge that its approved or cleared product was being prescribed or used for an unapproved use was sufficient to trigger the requirement to provide adequate labeling.

Industry groups say there is no support in the law for the “totality” standard and have asked the FDA to stay the rule indefinitely. The groups also oppose it because the FDA did not offer the totality standard as an option in the 2015 proposed rule, so it has not been subject to public comment. It may be that Gottlieb’s influence is already being felt at the FDA, even though he had not been confirmed by the Senate when the agency delayed the effective date of the rule on March 20, citing a petition of protest from PhRMA and others. The new effective date is March 19, 2018. In the meantime, the FDA will take public comment on the “important substantive issues” raised by the petition.

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REFERENCES
