Regulation of Pharmacoeconomics and Outcomes Research

Presented at the ISPOR 5th Annual International Meeting, Crystal City, VA, 24 May 2000

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Keywords: FDA, outcomes research, pharmacoeconomics, regulation

Introduction

Outcomes research, including pharmacoeconomic and health economic research, is conducted to provide stakeholders (patients, physicians, institutional providers, health benefit plan decision-makers, government authorities) with information about the value of pharmaceuticals, medical devices and medical procedures. Outcomes research is valuable to a stakeholder only if the data are relevant for that stakeholder and the information is received at a time and in a format that can assist the stakeholder in a decision about the use of the product or service. Outcomes research information is not useful if it has limited application (e.g., the cost data do not apply to the stakeholder’s setting) or it is received after a decision about the use of the product or service has been made.

Under our current system of health care delivery, outcomes research can be especially useful at the time a new product is introduced; a time when physicians, providers, patients and payers all have questions about the clinical and economic impact of a new treatment on the management of patients with the target disorder. At the time a new product is introduced, most of the data about it will have been gathered under the sponsorship of a corporate developer (pharmaceutical, biotechnology or medical device manufacturer). These corporate developers are regulated by the US Food and Drug Administration (FDA), and the dissemination of outcomes research information by these companies must comply with applicable FDA rules. When do those rules apply and what are the standards for dissemination of outcomes research information?

FDA Regulation of Promotional Communications

FDA only regulates communications by those who commercialize drugs, biologicals or medical devices in interstate commerce. FDA does not regulate scientific communications among researchers or practitioners. The two critical factors in analyzing whether FDA jurisdiction applies are: 1) commercialization and 2) interstate commerce. In theory, physicians and institutional providers may be viewed as commercializing products if they are in the chain of distribution of a product (e.g., hospitals with their own pharmacies selling to patients). However, FDA has only very rarely held providers to the same requirements to which product manufacturers are held, for example, where providers advertise that they provide a particular product. In today’s global economy, the interstate commerce requirement is nearly always met.

As well, the FDA does not regulate all communications by product manufacturers. FDA only regulates promotional communications. Which communications are promotional? Some are clearly promotional, such as product advertisements. Some communications are just as clearly not promotional, such as a manufacturer responding to an unprompted telephone call from a physician inquiring about any available clinical literature on an off-label use of marketed product. Other communications may...
be less clear whether or not they are promotional. For example, when a manufacturer sponsors a continuing education program, is that promotional? It depends whether the manufacturer has control over the content of the program. In such a case it is likely that the program would be considered promotional. If the manufacturer simply provides funding for a program but leaves decisions about the content of the program to an independent continuing education provider, the program likely would not be considered promotional.

In general, communications coming from or sponsored by a product manufacturer can be separated into two categories:

- promotional communications intended to advance the commercial success of a product;
- other nonpromotional communications, which may include medical communications in response to physician requests for information, scientific communications about research at professional meetings, and communications responding to requirements from governmental agencies.

What is the role of the FDA in regulating promotional communications? The Federal Food, Drug and Cosmetic Act prohibits the dissemination of promotional materials that are false or misleading (21 USC §352(a)). If a manufacturer disseminates information about a product that the FDA considers false or misleading, the product may be considered misbranded, and the FDA can take action against the product manufacturer. Penalties can range from requiring the manufacturer to stop disseminating the false information to seizure of the product or criminal penalties.

The historical standard used by the FDA to determine whether information about a product was false or misleading was the presence of “substantial evidence” established by “adequate and well-controlled trials.” This generally meant that a manufacturer was required to have data from well-controlled trials—usually randomized controlled trials or RCTs—to support each statement about a product used in promotional communications. This is still the standard applied when assessing the adequacy of substantiation supporting promotional claims concerning the safety or effectiveness of a product.

**FDA Regulation of Outcomes Research Communications Under FDAMA Section 114**

As the importance of pharmacoeconomic and outcomes research information has increased over the last 10 years, it has become clear that the standard of adequate and well-controlled trials does not work well for many economic analyses. Is resource utilization information sufficient when collected from a classic well-controlled RCT? Is there an adequate and well-controlled method of assigning costs from a payer database? It is difficult to fit economic models to an adequate and well-controlled trials standard because economic models inherently require extrapolation from clinical events shown in well-controlled trials to other endpoints (longer-term follow up, uncontrolled settings).

To address concerns that FDA regulation was limiting the development and dissemination of outcomes research, Congress included a section in the 1997 Food and Drug Administration Modernization Act (FDAMA) which set a standard different from the adequate and well-controlled trials standard for promotional dissemination of health care economic information to managed care organization formulary committees: “competent and reliable scientific evidence” (21 USC §352(a) as amended by Section 114 of PL 105–115 and commonly referred to as Section 114).

Although Section 114 did not require the FDA to promulgate regulations for the new standard to be effective, many in the outcomes research community felt it would be helpful for FDA to issue written guidance explaining the Agency’s understanding of the new law. To assist this process, the Health Outcomes Committee of the Pharmaceutical Research and Manufacturers Association (PhRMA) developed a draft guidance, which was submitted to FDA in June 1998. (http://www.PhRMA.org/issues/fda/6–22–98.html). In developing the draft guidance, the PhRMA group worked closely with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and sought input from ISPOR, the Society for Medical Decision Making, the Academy of Managed Care Pharmacy, the American Pharmaceutical Association, and other relevant groups.

In their draft guidance, PhRMA discussed the historical framework behind Section 114 and proposed guidance on the following terms in the new law:

- health care economic information;
- managed care or other similar organizations;
- formulary committee or other similar entity;
- directly related to an approved indication; and
- competent and reliable scientific evidence.

The PhRMA guidance took a broad, but reasonable, approach to interpretation of Section 114, consistent with the intent of Congress that Section...
Section 114 would increase the dissemination of outcomes research information by product manufacturers to managed care organizations.

The PhRMA Health Outcomes Committee concluded that the Section 114 term *health care economic information* should include all forms of economic analysis, allowing the guidance to adapt to the evolving discipline of outcomes research without requiring an update each time a new tweak on economic analysis methodology is published. Similarly, to meet changing arrangements between providers and payers, PhRMA proposed inclusion of all forms of managed care and any decision-making body within those using the categorizations *managed care or other similar organizations* and *formulary committee or other similar entity*. Under this proposal, a single individual such as a managed care medical director would be encompassed by the phrase *formulary committee, or other similar entity* if that individual had the authority to select products for plan beneficiaries.

One of the more difficult phrases to interpret in Section 114 is the limitation that promotion must involve a claim that *directly relates to an indication approved [by the FDA]*. In their draft guidance, PhRMA proposed that extrapolation from data included on labeling would be appropriate under the following circumstances:

- from duration of use in labeling to actual duration of use found in pharmacy utilization databases;
- from dosages included in labeling to actual dosages found in pharmacy utilization databases; and
- from clinical trial settings to actual practice settings.

The standard set by Section 114 of *competent and reliable scientific evidence* is the same standard used for years by the Federal Trade Commission (FTC) when assessing the adequacy of substantiation for manufacturer claims involving over-the-counter drug products and products affecting environmental health. That standard requires transparency of methods and conformance with methods accepted by experts in the field. The PhRMA proposal recommended that FDA follow long-established FTC practice in applying this new standard.

To date the FDA has not released its own guidance, nor has the Agency formally commented on the PhRMA proposal. The FDA has offered to discuss individual cases with manufacturers however, and FDA staff has been open and forthcoming in many professional meetings with their views and concerns about promotion of outcomes research information.

It is noteworthy that Section 114 only covers health economic data. Health-related quality of life (HRQoL) claims are considered to fall under the established *adequate and well-controlled trials* standard; FDA has been working on a guidance document addressing requirements for HRQoL claims, and publication of a draft document is expected shortly.

**ISPOR Section 114 Industry Survey**

Section 114 has been the law for over two years, but in the absence of formal guidance from FDA, many product manufacturers have been hesitant to develop promotional materials specifically for review under the Section 114 standard. In addition, as promotional materials are, by their nature, proprietary, little information is shared among companies about their experiences under Section 114. To understand better what manufacturers have experienced with respect to Section 114, ISPOR polled industry members in April 2000. The results were presented at the May 2000 International Meeting and were published recently [1].

Twenty-two individuals from 15 companies responded to the survey. As would be expected from ISPOR membership, respondents were from pharmacoeconomics or outcomes research departments. Of the 15 companies responding, 8 had submitted promotional outcomes research materials to FDA and 5 had received a response. In 3 of the 5 cases where a response was received, FDA permitted the sponsor to use the promotional materials; in two other cases, FDA required major modifications if the materials were to be considered acceptable for promotional use. Only one company reported having submitted proposed labeling claims covering health care economic information to FDA; 5 companies reported submitting HRQoL labeling claims to FDA. Most companies reported having received unprompted requests for health care economic information, and nearly all of those companies have responded through their medical communications departments.

**Conclusions**

Outcomes research information is useful only if it provides relevant information to stakeholders and is received in a timely fashion by stakeholders having to make decisions about a particular product or service. Traditional FDA regulation of promo-
tional communications by product manufacturers may restrict dissemination of useful outcomes research information. The intent of Section 114 of FDAMA was to improve the flow of outcomes research information by setting a different standard for testing the adequacy of health care economic information—competent and reliable scientific evidence—from the standard used for claims of effectiveness and safety—substantial evidence from adequate and well-controlled trials.

Although PhRMA has submitted a proposed guidance to clarify the terms of Section 114, FDA has not commented formally on the PhRMA submission, nor yet released its own guidance in this area. In the absence of formal guidance, few manufacturers are taking full advantage of Section 114. Nevertheless, there have been a modest number of submissions made to FDA under Section 114, and it appears that manufacturers and the FDA have to some degree begun to approach agreement about promotional use of outcomes research information. Hopefully, the FDA draft guidances on health care economic information and HRQoL will be released in the near future for public comment.

References
1 Smith MD, Long ET. FDAMA Section 114 Revisited: ISPOR surveys the pharmaceutical industry. ISPOR News 2000;6(4):5–6.