By Richard Lem, PharmD

In 1997, the US Congress passed the Food and Drug Administration Modernization Act (FDAMA), which modified the Federal Food, Drug, and Cosmetic Act (FD&C Act) to include several provisions reflecting the changing healthcare landscape of the late 1990s. However, 16 years later, one section of the law is still a subject of much debate within the industry. FDAMA Section 114 outlines the standard of evidence the pharmaceutical industry must meet to promote healthcare economic information (HCEI) regarding prescription drugs to managed care organizations and others. Section 114 states:

Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an [approved indication] for such drug and is based on competent and reliable scientific evidence. The requirements set forth in section 505(a) or in section 351(a) of the Public Health Service Act shall not apply to healthcare economic information provided to such a committee or entity in accordance with this paragraph .... The term ‘healthcare economic information’ means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another healthcare intervention, or to no intervention.¹

After the passage of FDAMA, FDA never drafted regulations or guidance that further defined the standards that must be met for HCEI in a promotional context. In addition, as of September 2013, there has yet to be a single untitled letter or Warning Letter that directly references Section 114.²

In general, efficacy or safety claims in promotional materials for prescription drugs and biologics should be supported by “substantial evidence.”³ The FD&C Act defines
“substantial evidence” as at least two adequate and well-controlled studies, or one adequate and well-controlled clinical investigation and confirmatory evidence. FDA regulations generally define an “adequate and well-controlled clinical trial” by seven key factors:

1. a clear study objective and a summary of the proposed or actual methods of analysis
2. inclusion of a control arm
3. confirmation that the study population has the disease or condition being studied
4. randomization
5. blinded design to minimize bias
6. a well-defined and reliable assessment of the response
7. an adequate analysis of the study’s result to assess the drug’s effect

In contrast, FDA has not issued a definition of “competent and reliable scientific evidence.” The standard has been defined by the Federal Trade Commission (FTC) as “evidence based on the expertise of professionals in the relevant areas that has been conducted and evaluated in an objective manner by qualified persons to do so, using procedures generally acceptable in the profession to yield accurate and reliable results.” FDA has not formally recognized FTC’s definition.

While FDA has not issued an official position on HCEI, the Office of Prescription Drug Promotion (OPDP) within the agency’s Center for Drug Evaluation and Research (CDER), has issued enforcement letters for promotional pieces that contain HCEI. A recent illustration is an untitled letter issued to Cumberland Pharmaceuticals Inc. in 2010. In the sales aid, a chart details the difference in treatment costs for hospitals between intravenous and oral N-acetylcysteine (see Figure 1).

If the sole intended audience of this sales aid was a managed care organization or formulary committee, the cost comparison may have been aligned with the provisions in
FDAMA Section 114, as it represents an “analysis that...compares the economic consequences...of the use of a drug to the use of another drug” and was “provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations.” However, OPDP was concerned that the clinical claims presented in the pharmacoeconomic analysis were not supported by substantial evidence. OPDP commented that the “pharmacoeconomic model assume[d] equivalent efficacy.”7 In other words, by comparing the costs of two treatments, the analysis implied they were equally efficacious. OPDP therefore considered the comparison of costs to be an unsubstantiated superiority claim, and was misleading because no adequate and well-controlled head-to-head trial had been conducted.8

**2013 Survey Underscores Industry Implementation of FDAMA Section 114**

In April 2013, the author conducted a survey to gauge how the industry approaches the promotional requirements for HCEI. A request was sent out to 108 professionals in various functions involved in promotional review or managed care with an open invitation to forward the survey to any colleagues interested in the subject matter. After two weeks, the pre-determined duration of the survey, 10 responses had been received. Of those, one responder did not specify job role; consequently, these responses were removed from the results of the survey.

Eight of the nine respondents did not believe there has been sufficient guidance about what competent and reliable scientific evidence encompasses. Six stated that their companies have a policy regarding FDAMA Section 114, and seven of nine responses indicated that materials directed toward managed care organizations were subject to promotional review. All but one respondent noted they would like more alignment between pharmaceutical companies and government agencies for healthcare economic information standards. A full review of the results can be found in Table 1 and Table 2.

The respondents also were given the opportunity to present their definitions of competent and reliable scientific evidence. Based on the results, there does not appear to be

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**Table 1.**

<table>
<thead>
<tr>
<th>What is your current role in the industry?</th>
<th>Do you believe that there has been sufficient guidance regarding what “competent and reliable scientific evidence” encompasses?</th>
<th>Does your company have a policy based on regulations set forth by FDAMA Section 114?</th>
<th>Managed care directed material are subject to:</th>
<th>Do you believe there should be alignment regarding standards between pharmaceutical and government agencies for healthcare economic analysis standards?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory Affairs</td>
<td>No</td>
<td>Yes</td>
<td>Promotional Review</td>
<td>Yes</td>
</tr>
<tr>
<td>Medical Affairs</td>
<td>No</td>
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<td>Regulatory Affairs</td>
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<td>Regulatory Affairs</td>
<td>Yes</td>
<td>No</td>
<td>Promotional Review</td>
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</table>

*Responders failed to submit answer (Promotional review, Compliance review, No internal review is required, other [open field])
consistency in their definitions. Answers ranged from broad and situational—relying on medical affairs to verify that the data are robust and scientifically sound; to very specific—an adequate and well-controlled trial (see Table 2).

**Conclusion**

Even with such a small turnout, the survey effectively illustrated the diverse interpretations of the standards for HCEI in a promotional setting. Fortunately, HCEI seems to be on OPDP’s radar. At the Food and Drug Law Institute’s Advertising and Promotion Conference in September 2013, Thomas Abrams, director of OPDP stated that HCEI is the subject of possible future guidance.9 As healthcare cost discussions become more prevalent in the US, specific guidance from FDA regarding the level of evidence required for promotional materials containing HCEI claims would be immensely helpful for the industry.

**About the Author**

Richard Lem is completing a two-year Biogen Idec post-doctoral fellowship in regulatory affairs—advertising, labeling and promotion. Lem received his PharmD from Ernest Mario School of Pharmacy at Rutgers University and is a registered pharmacist in the states of New Jersey and Massachusetts. He can be reached at Richard.Lem@biogenidec.com.

**References**

1. *FD&C Act* § 502(a); 21 USC 352(a) (as modified by *FDAMA* §114).
4. *FD&C Act* § 505(d); 21 USC 355(d) (as modified by *FDAMA* §115).
5. *FD&C Act* § 502(a); 21 CFR 314.126.


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