FDAMA 1997 Section 114: Another Look
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ABSTRACT
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ARTICLE TEXT
Under the FDA Modernization Act of 1997 (FDAMA), certain "health-care economic information" is permitted to be distributed by pharmaceutical manufacturers to defined categories of managed care decision makers [1]. The statute provides that certain health-care economic information (HCEI) shall not be considered false and misleading if it is based upon "competent and reliable scientific evidence," rather than the normal (and higher) standard of "adequate and well-controlled trials" (also known as substantial evidence). However, HCEI qualifies for this relaxed standard of proof under the statute only if the information "directly relates to an indication approved under Section 505 [of the FD&C Act] or under Section 351(a) of the Public Health Service Act . . ." [1].

It is clear from the legislative history that Congress was willing to accept less restrictive treatment of HCEI only with respect to approved indications [2]. This requirement provided assurance that any efficacy claims incorporated into HCEI would already have been demonstrated through adequate and well-controlled trials. FDAMA clearly does not permit a manufacturer to promote an efficacy claim that would otherwise be prohibited through "gamesmanship"—that is weaving an unapproved claim together with economic data and characterizing the mixture as "health-care economic information."

Food and Drug Administration (FDA) carefully limits a drug's labeling to the health claims proven by well-controlled studies. If a particular drug is clinically shown to have a beneficial effect only on surrogate markers (e.g., blood pressure, cholesterol reduction), the drug's labeling is limited to claims about these surrogates, and the applications of HCEI should align with the approved labeling as well. The nature of the end points in approved labeling was an important aspect of the congressional deliberations concerning Section 114. One key issue related to the implementation of Section 114 concerns the use of HCEI to characterize the value of incremental effectiveness on a surrogate measure relative to the incremental cost to achieve that value; HCEI metrics that align with end points in approved labeling would appear to meet the intent of the legislation. While the representation of relative value concerning surrogate end points would probably meet the Section 114 criteria, it would be more limited and enable relative value assessments only within the evidentiary boundaries of similar end points supported with similar labeling. Relative value associated with a specific end point might run counter to a quality-adjusted life-year (QALY)-only policy that is intended to
represent relative value in the same currency across all interventions regardless of end point. On the other hand, if an new drug application (NDA) sponsor performed clinical studies demonstrating a beneficial impact on health outcome (HO) end points (e.g., reduction in mortality and major morbidity) which were reflected in the drug's label, these could be reflected in QALY and life-year gained metrics. Finally, allowing extrapolated HO claims to be incorporated into HCEI without evidence of reduction in major morbidity and mortality could dilute the incentive for manufacturers to perform event-related end point studies.

Five examples of end points were provided in the House Report on FDAMA to provide insights concerning the criteria that HCEI be directly related to an approved indication [2]. The examples illustrate the intent of Congress to align the evidence of benefit in an approved indication as an important part of the generation of HCEI that is competent and reliable.

Quoting directly from the congressional record:

The proposal defines "health-care economic statement" as any analysis that identified, 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 health-care intervention, or to no intervention.

The provision is limited to analyses provided to such entities because such entities are constituted to consider this type of information through a deliberative process and are expected to have the appropriate range of expertise to interpret health care economic information presented to them to inform their decision-making process, and to distinguish facts from assumptions.

The provision is not intended to permit manufacturers to provide such health care economic information to medical practitioners who are making individual patient prescribing decisions nor is it intended to permit the provision of such information in the context of medical education.

To illustrate this point, economic claims based on preventing disease progression would ordinarily not be considered to be directly related to an approved indication for the treatment of symptoms of a disease, for a drug for which the use in prevention of disease progression has not been approved.

There were five clinical examples in the congressional record (numbers and bold added):

1. For example, rheumatoid arthritis drugs are approved for the treatment of symptoms and not for the prevention of deformity. Therefore, economic claims based in part on an assumption of prevention of deformity would not be considered directly related to the approved indications for these drugs.
2. Similarly, economic claims based on prolonging patient survival would not be considered directly related and would not, therefore, be permitted under this subsection, for agents approved for the symptomatic treatment of heart failure, but not approved for prolonging survival in heart failure patients.

3. For example, modeling the resource savings of insulin therapy to achieve tight control of blood sugar in type 1 diabetes could include cost savings associated with prevention of retinopathy (an eye disease) and nephropathy (kidney disease) based on well-controlled study(ies) that demonstrate that control of blood sugar levels with insulin leads to a reduction of such consequences. Because prevention of retinopathy and nephropathy could not simply be assumed to be a result of blood sugar control, these prevention claims would have to be shown by well-controlled study(ies) before inclusion as health-care outcome assumptions.

4. In contrast, economic claims that model, based on observational studies in a population of women, the economic consequences of prevention of fractures due to osteoporosis would be permitted for drugs already approved for prevention of fractures due to osteoporosis. This is possible because observational data may be considered competent and reliable for making an assumption about the secondary consequences of an osteoporotic fracture once the primary prevention has been established.

5. Similarly, the long-term economic consequences of the prevention of meningitis by haemophilus b influenza vaccine could be modeled using population-based data once the primary prevention claim is established.

These five clinical examples provide insights into the congressional intent for Section 114 applications. One issue for the HO community is the form that an HCEI analysis should take relative to the substance of clinical evidence. The congress, with the FDA's input, felt that the clinical evidence should ground the discussion of care choices, despite the fact that no formal guidance concerning Section 114 has been issued to date. Many HO interest groups appear less concerned with the clinical evidence, the effectiveness denominator of the incremental cost effectiveness ratio (ICER), and more concerned with the form—that the denominator be a QALY and thus enable universal relative value assessments.

When the FDA awards a claim for a drug, they have reasonable confidence that the claim is not false or misleading based upon the evidence of effectiveness. Under 114 criteria, they are not willing to allow surrogate-level evidence to be extrapolated to event-level characterization of effectiveness. Two evidence issues for the HO community are: 1) should the level of evidence (i.e., surrogate or event) influence the choice of a HO metric; and 2) is a utility a valid and reliable means of adjusting for effectiveness across end points that may represent surrogate or event-level outcomes?
A comparison of relative change based upon the same surrogate in similar trial settings would appear to meet the intent of the 114 legislation, while projecting risk reduction on the basis of a change in a surrogate measure (e.g., blood pressure or cholesterol) and comparing that measure of effectiveness to a finding of risk reduction in an event trial (e.g., heart attacks, strokes, and death) would appear to run counter the legislative intent. Does the HO community have reasonable confidence that a QALY is not false or misleading? At an annual ISPOR meeting, I attended a presentation where a QALY for an erectile dysfunction drug was compared to a QALY for a statin in the setting of secondary prevention of heart disease events. While the QALYs were roughly similar in amount, the effectiveness foundations for relative value were very different with one relying primarily on a relative change in a utility and the other on a relative reduction in the composite rate of heart attacks, strokes, and death. To promote competent and reliable comparisons, perhaps it is time to give Section 114 another look.

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References

1. FDAMA §114; 21 USC 352(a).