Health Policy Analysis

When Does FDAMA Section 114 Apply? Ten Case Studies

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ABSTRACT

Background: Section 114 of the Food and Drug Administration Modernization Act of 1997 regulates the promotion of health economic information by pharmaceutical companies to US health plans. Greater clarity is important given demands by payers and other stakeholders for evidence of value. Objectives: To develop hypothetical case studies of health economic promotions to examine legal and policy implications. Methods: We constructed for pedagogical purposes 10 categories of potential health economic promotions. We generated hypothetical case studies for each category, including questions about whether each might be allowable under Section 114. The case studies were developed around the following categories: 1) costing out on-label clinical end points; 2) promotion of a costing exercise to physicians working in an accountable care organization setting; 3) burden-of-illness claims; 4) economic analysis of a formulary restriction policy; 5) extrapolations to doses, populations, or settings not covered in trials; 6) adherence claims; 7) “utilization of care” as a secondary end point in randomized clinical trials; 8) costing out a competitor drug’s adverse event; 9) economic analysis of comparative effectiveness claims using an indirect treatment comparison; and 10) extrapolating from surrogate to long-term outcomes in an economic model. Discussion: Most cases seem to fall into a gray zone given haziness around what constitutes “competent and reliable evidence” and “directly relate[d]” to an approved indication. In practice, it is difficult to know what the section allows given the imprecision of the statute and lack of guidance about its scope. Conclusion: Ideally, future guidance will provide clarity and flexibility.

Keywords: case studies, competent and reliable scientific evidence, FDAMA Section 114, health economics, United States.

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Introduction

Section 114 of the Food and Drug Administration Modernization Act of 1997 stipulated the circumstances under which pharmaceutical companies can proactively promote health economic information to health plans. The idea was to permit flexibility so that companies could engage health plans to inform coverage and reimbursement. The Food and Drug Administration (FDA), however, has never released guidance or issued regulatory action on this topic. Clarity is important given the growing interest by payers and other stakeholders for evidence of value using real-world databases and comparative effectiveness research [1].

The section contains four key provisions (Table 1). First, the law applies only to “health care economic,” not clinical, information. Second, a promotion must target a “formulary committee or other similar entity.” Third, support for the claim must comprise “competent and reliable scientific evidence” (CRSE), rather than “substantial evidence,” the standard governing clinical promotional claims to general prescribers [2]. CRSE suggests a more flexible criterion than the substantial evidence standard for clinical claims, which generally means two adequate and well-controlled clinical trials. However, CRSE should not be seen as a path to compromise scientific integrity. Rather, the competent and reliable standard refers to a set of best practices criteria that support that health economic information intended for promotional purposes. Such practices would presumably include that studies should conform to proper methodological practices [3–7]; have prespecifed end points, a scientifically sound research design and analysis plan, and a strong statistical foundation—for example, sufficient attempts to control for bias; and rule out potential confounders. Sensitivity analyses should be carried out, results should be appropriately generalizable, and analyses should be conducted as prespecified, without inspection of comparative outcomes. Importantly, studies must still adhere to FDA’s criteria for “fair balance,” meaning that associated advantages and risks must be communicated via reasonably similar substance and format.

Fourth, promotions must “directly relate[d]” to an approved drug indication. The directly-related provision is important in signaling that Section 114 was not intended as a path to “off-label” promotion. What is meant by “directly relate,” however, is not entirely clear. Virtually all health economic analyses rest on a clinical foundation and frequently include implied or explicit assumptions about a product’s risks and benefits in certain populations and over certain time periods. A House Committee...
the lack of FDA guidance and uncertainty about where the maneuverability owing to the restrictiveness of the provisions, that attention to Section 114, including that the section provides limited observers have suggested several potential reasons for the lack of constrain their ability to change them later.

Although drug companies supposed to have conducted a study by 2002, but it never did. any public statements from FDA officials about Section 114, however, have been rare and those made, though they represent the views of the individual making them and not necessarily the FDA, seem to suggest a high evidence bar for Section 114—for example, by suggesting that comparative claims generally require substantial evidence from a head-to-head comparison [9]. relatively little has been written about Section 114. According to the authorizing statute, the Government Accountability Office was supposed to have conducted a study by 2002, but it never did. although drug companies have promoted claims about costs and value in print advertisements [10], the extent to which companies are using Section 114 is not clear. no one really knows the extent to which companies use Section 114, because the FDA does not publish any information about who has contacted it on Section 114 initiatives. moreover, to our knowledge, FDA has never taken any action in the form of a warning letter or notice of violation against a company that specifically mentions a violation of the Section 114 statute [11]. two surveys of outcomes research leaders in pharmaceutical companies suggested that drug firms are using Section 114 to some extent, but that companies are cautious and want more clarity from the FDA, particularly about how to define CRSE [2,12]. observers have suggested several potential reasons for the lack of attention to Section 114, including that the section provides limited maneuverability owing to the restrictiveness of the provisions, that the lack of FDA guidance and uncertainty about where the “line” is have made companies wary of using the section, and that unsolicited requests by health plans for information about value through the Academy of Managed Care Pharmacy Format has co-opted the section [13]. other reasons companies may not want to use Section 114 may include their lack of expertise or experience in the area, the time and risks involved, and, possibly, that they are successful with other marketing strategies and do not see the need. Companies may also be cautious about using Section 114 because of concern that if they reveal drug prices in a pharmacoeconomic analysis, it may constrain their ability to change them later.

to illuminate situations in which Section 114 may apply, we developed 10 hypothetical case studies. to our knowledge, this is the first effort to develop such examples and explore the potential legal and policy implications. Our intention is to advance understanding around Section 114 and to stimulate debate on regulatory and legislative responses. the intended audience consists of 1) individuals within pharmaceutical companies who develop evidence and consider promotional materials containing health economic information and 2) the FDA and legislators, who must interpret the appropriate boundaries of Section 114. the article also has implications for payers and formulary committee members, who are the recipients of Section 114 promotions.

## Methods

### Constructing Categories of Health Economic Promotions

on the basis of our experiences interacting with pharmaceutical companies on issues surrounding Section 114, we developed the following examples:

- Costing out on-label clinical end points
- Promotion of costing exercise to physicians working in accountable care organization (ACO) settings
- Burden-of-illness claims
- Economic analysis of a formulary restriction policy
- Extrapolations to doses, populations, or settings not covered in trials, but reflecting how drugs are used in the real world
- Adherence claims
- “Utilization of care” as a secondary end point in randomized clinical trials
- Costing out a competitor drug’s adverse event
- Economic analysis of comparative effectiveness claims using an indirect treatment comparison
- Extrapolating from surrogate to long-term outcomes in an economic model

The 10 examples are listed roughly in order of proximity to the drug’s labeled clinical claim; that is, earlier examples contain promotions closer to labeled claims. in constructing the categories, we sought to cover a range of issues based on study designs, databases, and end points.

### Developing Case Studies

we generated hypothetical case studies for each category. for each case, we highlight key issues (Table 2) and also present the cases in terms of their distance from the labeled clinical indication (Fig. 1). all cases are hypothetical and by necessity oversimplified. they were developed for pedagogical purposes. we emphasize that in reality, submission to the FDA using Section 114 submissions may be part of a larger and more complex exercise that includes considerations of efficacy, safety, effectiveness, coherence with the label, highlights of findings, methods, means, interpretations, and plans for promotional use. in this article, we have focused only on the health economic claim. however, we attempted to make these claims as relevant as possible to real-world situations. we also attempted to cover a range of diseases (e.g., chronic vs. acute) and situations (e.g., use of databases and indirect treatment comparisons). to check the plausibility and verisimilitude of the cases, we shared an early draft of the article with both the national pharmaceutical council, who provided support for this research, and the office of prescription drug promotion at the FDA. with our agreement, the national pharmaceutical council, in turn, shared the draft with its member companies for review, and we received comments from seven companies. we did not receive feedback from the FDA other than an acknowledgment that it had received

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**Table 1 – Key issues in FDAMA Section 114.**

<table>
<thead>
<tr>
<th>Key issue</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care economic information</td>
<td>Claims must pertain to the health care economic information associated with using a particular drug (not clinical efficacy)</td>
</tr>
<tr>
<td>Audience</td>
<td>Claims must be directed to a formulary committee or similar (presumably population-level decision makers), not to providers, consumers, or patients</td>
</tr>
<tr>
<td>Competent and reliable scientific evidence</td>
<td>Claims must meet this standard of evidence, presumably by meeting the standards of experts in the field, rather than the stricter “substantial evidence” standard for clinical claims (generally two adequate and well-controlled trials)</td>
</tr>
<tr>
<td>Directly related to the approved indication</td>
<td>Claims must be directly related to an indication for which the drug has been approved by the FDA</td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; FDAMA, Food and Drug Administration Modernization Act of 1997.
Table 2 – Case studies.

<table>
<thead>
<tr>
<th>Category</th>
<th>Promotional claim</th>
<th>Key issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Costing out on-label clinical end points</td>
<td>• Is Section 114 even needed?</td>
</tr>
<tr>
<td></td>
<td>A Medicare advantage plan of 1 million enrollees would save roughly $3 million over a 1-y period because of reduced hip and vertebral compression fractures in its population.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Promotion of costing exercise to physicians working in ACO settings</td>
<td>• Is the physician an acceptable audience covered under the “formulary committee or other similar entity” provision?</td>
</tr>
<tr>
<td></td>
<td>The ACO would save $1.5 million over a 1-y period because of reduced hip and vertebral compression fractures in its population due to drug A.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Burden-of-illness claims</td>
<td>• Does the burden-of-illness claim fall under Section 114?</td>
</tr>
<tr>
<td></td>
<td>RRMS is an expensive disease, costing roughly $30,000 per patient per year above the cost of care for matched controls.</td>
<td>• Do burden-of-illness claims imply clinical claims?</td>
</tr>
<tr>
<td>4.</td>
<td>Economic analysis of a formulary restriction policy</td>
<td>• What if, as is inevitable, the patients in the database on which the study is based differ from those in the trial (e.g., they have different RRMS symptoms)?</td>
</tr>
<tr>
<td></td>
<td>Formulary access restrictions on biologic C increase overall health costs.</td>
<td>• Does the methodology adhere to the CRSE standard?</td>
</tr>
<tr>
<td>5.</td>
<td>Extrapolations to doses, populations, or settings not covered in trials, but reflecting how drugs are used in the real world</td>
<td>• Is an implied claim of effectiveness being made about populations unlike those in the RCT?</td>
</tr>
<tr>
<td></td>
<td>Use of drug E saves $500,000 for a health plan over a 1-y period.</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Adherence claims</td>
<td>• Are adherence claims covered under Section 114?</td>
</tr>
<tr>
<td></td>
<td>In a health plan database, in patients with Parkinson’s disease, drug F is associated with higher rates of adherence than drug G over a 1-y period.</td>
<td>• Does the promotion make unsubstantiated implied clinical claims?</td>
</tr>
<tr>
<td>7.</td>
<td>”Utilization of care” as a secondary end point in RCTs</td>
<td>• Is length of stay covered under Section 114?</td>
</tr>
<tr>
<td></td>
<td>A retrospective database study showed that in patients with certain hospital-acquired infections, drug H reduces hospital length of stay and would save a midsize hospital $400,000 per year.</td>
<td>• Is there an implied clinical claim of superiority?</td>
</tr>
<tr>
<td>8.</td>
<td>Costing out a competitor drug’s adverse event</td>
<td>• Is there an implied clinical claim of superiority?</td>
</tr>
<tr>
<td></td>
<td>In a retrospective database study, drug J reduces costs of hospitalizations due to infection by $500 per patient over 1 y relative to drug K.</td>
<td>• To what extent is it problematic that the trial was not and could not be powered to examine adverse events?</td>
</tr>
<tr>
<td>9.</td>
<td>Economic analysis of comparative effectiveness claims using an indirect treatment comparison</td>
<td>• Does the promotion go beyond health economic data because of the implied clinical claim of superiority from the indirect treatment comparison?</td>
</tr>
<tr>
<td></td>
<td>An indirect treatment comparison suggests that drug L reduces the cost of health care related to asthma in children aged 2 to 16 y relative to drug M.</td>
<td>• Does the indirect treatment comparison meet the CRSE standard?</td>
</tr>
<tr>
<td>10.</td>
<td>Extrapolating from surrogate to long-term outcomes in an economic model</td>
<td>• Would this claim violate the “directly-relate [d]” clause if the epidemiological evidence were very strong?</td>
</tr>
<tr>
<td></td>
<td>Drug N has an incremental cost-effectiveness ratio of $10,000 per QALY gained vs. standard of care in patients at risk for heart disease; it is considered cost-effective by traditional benchmarks.</td>
<td>• Does the modeling approach constitute CRSE?</td>
</tr>
</tbody>
</table>

ACO, accountable care organization; CRSE, competent and reliable scientific evidence; QALY, quality-adjusted life-year; RCT, randomized controlled trial; RRMS, relapsing-remitting multiple sclerosis.

and appreciated the article. All judgments and conclusions are those of the authors and do not necessarily reflect the views of the National Pharmaceutical Council or others.

Case Studies

Case 1: Costing out on-Label Clinical End Points

Rationale: A company wishes to “cost out” clinical end points from a randomized controlled trial (RCT).

Scenario: Company 1 conducts an RCT on drug A, with hip and vertebral compression fractures as primary end points. The drug is approved with an indication to prevent these fractures in postmenopausal women with osteoporosis. The company uses published estimates on fracture costs to estimate potential savings from using the drug, based on data on the drug’s effect in the clinical trial, for a typical health plan serving Medicare populations.

Promotional claim: A Medicare Advantage plan of 1 million enrollees would save roughly $3 million over a 1-year period.
because of reduced hip and vertebral compression fractures in its population owing to the use of drug A.

Key questions:

- Because the claim “costs out” clinical end points on the label, is it limited to Section 114 promotions, or could companies make this claim to general prescribers?
- Does the costing exercise comprise CRSE? What standards would the cost estimates have to meet? Is it sufficient to apply estimates from one context to an “average” population?

Analysis: This type of promotion might be allowable under Section 114 because it is a costing exercise pertaining to on-label claims, though presumably the exercise would have to conform to CRSE standards and perhaps the populations underlying the cost estimates would have to be applicable to other settings.

**Case 2: Promotion of Costing Exercise to Physicians Working in ACO Settings**

Rationale: A pharmaceutical company wants to promote a claim to a physician in an ACO, using the same exercise discussed above in case 1.

Scenario: As in case 1, company 1 conducts an RCT on drug A, with hip and vertebral compression fractures as primary end points. The drug is approved to prevent these fractures in postmenopausal women with osteoporosis. The company uses published estimates on fracture costs to estimate savings for an ACO with 500,000 patients. The company presents the analysis to a physician working in the ACO who participates in the organization’s management.

Promotional claim: The ACO would save $1.5 million over a 1-year period because of reduced hip and vertebral compression fractures in its population owing to drug A.

Key questions: Is the communication covered under the “formulary committee or other similar entity” provision of Section 114?

Analysis: Section 114 covers “formulary committee[s] or other similar entit[ies],” and whether the clause covers ACOs is not entirely clear. The phrase “similar entities” seems to imply organizations making population-based decisions, and thus the claim might be deemed allowable because it is presented to a physician in a management position in the organization. One might evoke a version of the “learned intermediary” legal doctrine, which holds that manufacturers of drugs fulfill their duty of care when they provide necessary information to experts who then interact with end users [14]. In this case, physicians working on behalf of the formulary committee, health plan, or ACO would be the learned intermediary, making an informed choice on behalf of the general prescribers in the organization as well as the patient populations served. Prescribers with no access responsibilities for other prescribers would not fall under Section 114. The physician in question, however, would be expected to serve in a management role and to have expertise to evaluate the evidence underlying the Section 114 promotion. Moreover, the company would be advised to approach the physician through the ACO’s committee membership and staff.

**Case 3: Burden-of-Illness Claims**

Rationale: A company wants to disseminate a burden-of-illness study to health plans.

Scenario: Company 2 markets drug B, indicated for alleviating tremor and fatigue, symptoms of relapsing-remitting multiple sclerosis (RRMS). The drug is not indicated for other symptoms, such as cognitive or visual impairment. The company analyzes a health insurance claims database to calculate the annual health care costs incurred by patients with RRMS compared with matched controls. There is no information in the database about
the symptoms, so the study relies on diagnosis codes for multiple sclerosis and assumptions about the proportion of patients with RRMS.

Promotional claim: RRMS is an expensive disease, costing roughly $30,000 per patient per year above the cost of care for matched controls.

Key questions:

- Is a promotional claim that does not include a drug covered under Section 114? According to the statute, health care economic information “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 health care intervention, or to no intervention.”
- Is there an implied clinical claim about drug B because it is indicated for certain symptoms (tremor and fatigue), whereas the burden was calculated using estimates of patients assumed to have RRMS (who thus likely had other symptoms as well)?
- Does the promotion potentially violate the “directly-related to an indication approved” provision?

Analysis: As with other examples, the case seems to fall in a gray area. This promotion might be permissible, because it does not make overt clinical claims about the drug and simply contains a cost-of-illness study. There could be questions, however, about whether a claim that does not include a drug falls under Section 114. In addition, there may be questions about whether there are implied clinical claims if the promotion appears linked to a particular product, and about whether the promotion is “directly relate[d]” to the approved indication because patients in the database have symptoms unlike those indicated for the drug. Also, the methodology would have to adhere to CRSE standards.

Case 4: Economic Analysis of a Formulary Restriction Policy

Rationale: A company believes that a health plan’s formulary restriction policy may increase overall health costs for affected patients.

Scenario: Company 3 has biologic C, which is indicated for reducing inflammation in rheumatoid arthritis. A health plan adds a step edit restricting access to biologic C, such that patients must first have an inadequate response to a less expensive drug D (approved for the same indication). The company hypothesizes that the policy will increase overall health costs, even though it may reduce pharmacy costs, because patients will be less well managed on the cheaper alternative, and thus have more physician visits and hospitalizations. The company conducts a retrospective analysis using claims data. It analyzes patients with at least one prescription of the drug and plan enrollment 1 year before and after policy implementation.

Promotional claim: Formulary access restrictions on biologic C increase overall health costs.

Key questions:

- Is there an implied clinical claim of superiority and thus a violation of the “directly-related” clause?
- Does the methodology adhere to the CRSE standard? What research design and statistical methods were used?

Analysis: This promotion might be allowable because it contains an analysis of a formulary restriction and does not make overt clinical claims. There may be concerns, however, about implied clinical claims of superiority, and potentially concerns that study populations may differ from those in the product label. Moreover, the methods would have to adhere to CRSE standards.

Case 5: Extrapolations to Doses, Populations, or Settings Not Covered in Trials, but Reflecting How Drugs Are Used in the Real World

Rationale: A company wishes to present a budget impact model (BIM) to a health plan.

Scenario: Company 4 has demonstrated in an RCT that drug E (an antiarrhythmic drug) is associated with fewer hospitalizations due to atrial fibrillation than a competitor in patients with a history of persistent atrial fibrillation. The company develops a BIM to show a health plan’s savings over 1 year from reduced hospitalizations.

Promotional claim: Use of drug E saves $500,000 for a health plan over a 1-year period.

Key questions: Does use of the BIM violate the “directly-related” clause of Section 114 because plan populations differ from those in the product label?

Analysis: The promotion might be allowable because the analysis assumes that the drug works in a similar way in the plan population as it did in the RCT. Concerns could arise to the extent that the populations differ—that is, in terms of demographic characteristics, disease severity, and treatment regimen or if the trial is done on selected subgroups but the BIM generalizes to broader populations—or if the analysis does not adhere to CRSE standards.

Case 6: Adherence Claims

Rationale: A new drug has similar efficacy to, and a higher price than, a competitor, but because of its dosing may be associated with higher adherence.

Scenario: Company 5 conducts an RCT that demonstrates that drug F is effective in controlling symptoms of Parkinson’s disease. Drug G is also indicated for Parkinson’s disease, but drug F and drug G were not compared in a head-to-head trial. Although they have similar efficacy, the more expensive drug F is dosed once a day versus three times per day for its competitor. Suspecting that this difference is associated with better adherence (and thus better outcomes and lower costs), the company analyzes a claims database to examine adherence rates in patients taking the drugs.

Promotional claim: In a health plan database, in patients with Parkinson’s disease, drug F is associated with higher rates of adherence than drug G over a 1-year period.

Key questions:

- Are adherence claims covered under Section 114?
- Does the promotion imply an unsubstantiated superiority claim?
- What methods must be used to ensure that the analysis complies with the CRSE criterion?
- If the company had calculated the cost differential associated with improved adherence and only used those savings estimates in the promotion, would it be allowed under Section 114?

Analysis: Whether the promotion would be allowed is unclear. One might argue that the design is not adequate given the potential for confounding. Moreover, adherence may not be covered under health economic data and one could argue that there are implied clinical claims of superiority of one drug over another. Adherence, however, can reflect many factors—efficacy, safety, costs, convenience, and so forth—and it is challenging to tease out determinants. Possibly, an “adherence” claim would be
permissible under the spirit of Section 114 as long as the analysis meets CRSE criteria (i.e., in this case a well-conducted database study) and there is no overt clinical claim of superior efficacy or safety. Furthermore, one could argue that clinical superiority is not implied, given that dosing differences in the case seem to underlie the improved adherence. An important part of the analysis would be ruling out any co-pay differences as a confounding factor. Finally, the FDA will likely scrutinize promotional claims involving head-to-head comparisons rigorously and perhaps more rigorously than non-head-to-head claims, and thus, additional issues about the claim in question might be raised.

Case 7: “Utilization of Care” as a Secondary End Point in RCTs
Rationale: A new drug has similar efficacy to and a higher price than a competitor, but may be associated with decreased hospital length of stay (LOS) and lower costs.

Scenario: Drug H from company 6 is approved on the basis of a noninferiority trial versus drug I in treating certain hospital-acquired infections including methicillin-susceptible and methicillin-resistant staphylococcus aureus bloodstream infections. In the trial, drug H reduces the LOS (a secondary end point) by 0.4 days. Separately, the company analyzes a claims database to examine the LOS in patients taking the two drugs and calculates that drug H reduces the LOS by 0.6 days relative to drug I and would save a midsize hospital $400,000 per year.

Promotional claim: A retrospective database study showed that in patients with certain hospital-acquired infections, drug H reduces hospital LOS and would save a midsize hospital $400,000 per year.

**Key questions:**
- Is LOS covered under Section 114?
- Is there an implied clinical claim of superiority? Does the fact that the LOS was prespecified as a secondary end point help? Would it matter if this result had been statistically significant? Does it matter if the LOS relates to the primary end point?

Analysis: Whether the promotion would be allowable is unclear. Although there are no overt clinical claims, one could argue that there is an implied superiority claim. It is also unclear whether LOS claims are covered under the section and whether a claim based on this secondary end point would be allowable. The concern about implied clinical claims might be considered weak if other factors (dosing differences, hospital policies) are probable causes of LOS differences and the claim may not meet CRSE standards if those other factors are not accounted for in the analysis.

Case 8: Costing out a Competitor Drug’s Adverse Event
Rationale: A new drug has efficacy similar to that of a competitor, but may have a better adverse events profile that results in lower costs.

Scenario: Company 7 conducts an RCT on drug J that demonstrates superiority to standard of care in reducing inflammation from rheumatoid arthritis. A separate trial studied drug K, in the same therapeutic class, with a similar population and comparator. Although there were no head-to-head trials, drug J had fewer adverse events, including fewer infections due to hospitalization. Company 7 analyzes patients on each drug in a claims database and compares hospitalizations due to infections over 1 year. The company calculates that patients taking drug J have fewer hospitalizations due to infection and $500 less per patient in hospitalization costs over the year.

Promotional claim: In a retrospective database study, drug J reduces costs of hospitalizations due to infection by $500 per patient over 1 year relative to drug K.

**Key questions:**
- Does the promotion lack adequate substantiation because of the implied clinical claim of superiority from the indirect treatment comparison?
- Does the indirect treatment comparison meet the CRSE standard?

Analysis: Although the permissibility of the claim is subject to some debate, presumably this type of promotion raises questions because there are implied superiority claims without direct comparisons in clinical trials or real-world databases. The indirect treatment comparison would have to meet CRSE standards, but even a well-done analysis that focuses on cost would not completely remove concern about implied clinical claims without head-to-head RCTs.

Case 9: Economic Analysis of Comparative Effectiveness
Rationale: A company wants to promote the economic advantages of its drug against a competitor. The two drugs, however, have not been compared in head-to-head trials, so the company conducts a comparative effectiveness study.

Scenario: Company 8 markets drug L, which has demonstrated superiority to standard of care in reducing asthma inflammation and symptoms in children aged 2 to 16 years. A competitor in the same therapeutic class, drug M, is approved for the same indication against the same comparator. Company 8 conducts an indirect treatment comparison using data from the separate trials and finds that drug L reduces asthma attacks and decreases symptom severity relative to drug M. The company calculates associated costs using published estimates on acute asthma exacerbation costs.

Promotional claim: An indirect treatment comparison suggests that drug L reduces the cost of health care related to asthma in children aged 2 to 16 years relative to drug M.

**Key questions:**
- Does the cost comparison imply clinical superiority?
- Would use of the database raise any concerns because it contains patients who differ from those in the trial?

Analysis: As in other examples, the promotion seems to fall in a gray area. There are no overt clinical claims made and the drugs in questions have similar indications and were studied on similar populations and comparators. Because the database analysis follows the drug’s approved indication, the use of the claims data would presumably not raise concerns. Even if done according to CRSE standards, however, the analysis may raise questions about implied clinical claims of superiority given the absence of direct comparisons in trials. As noted above, the FDA may view the absence of head-to-head trials as a particular problem.

Case 10: Extrapolating from Surrogate to Long-Term Outcomes in an Economic Model
Rationale: A company develops an economic model to estimate the long-term consequences of using its drug.

Scenario: Company 9 markets drug N, indicated to lower lipid levels in individuals diagnosed with, or at risk for, heart disease. The company develops a model to estimate the cost per quality-adjusted life-year associated with drug N. Because no RCT has examined the impact of drug N on cardiovascular events (myocardial infarction, stroke, etc.) and mortality, the company uses published risk equations based on well-established epidemiological evidence demonstrating the association between lipid levels and cardiovascular events and mortality. Cost information is derived from a claims database and national data on event costs.
Quality-adjusted life-year calculations are based on published estimates of health utilities for cardiac events and other relevant health states.

Promotional claim: Drug N has an incremental cost-effectiveness ratio of $10,000 per quality-adjusted life-year gained versus standard of care in patients at risk for heart disease; it is considered cost-effective by conventional benchmarks.

Key questions:

- Would a promotional claim based on this model violate the “directly-related” clause? What if the epidemiological evidence linking lipids and cardiac events were extremely robust and the model contained a disclaimer that the company had not studied the long-term end points in trials?
- What model development standards would meet the CRSE standard?

Analysis: Whether the promotion of this model under Section 114 would be allowable is unclear, but the case raises questions because it may violate the “directly-related” clause in extrapolating from intermediate to long-term end points not on the label. It also uses information from databases that contain patients unlike those studied in the clinical trial. Whether the model meets the CRSE standard will presumably turn on factors such as transparency of the assumptions, the appropriateness of the methods and inputs, and the presence of sensitivity analysis (e.g., see the report on modeling practices by ISPOR and SMDM) [15].

Discussion

The case studies illustrate a range of possible health economic promotional claims and highlight possible interpretations regarding Section 114. However, with the possible exceptions of cases 1 and 2, the strictest interpretation of the section might prohibit most examples, because the underlying analyses diverge from “substantial evidence” and potentially contain implied clinical claims, even if they are remote and even if the analyses underlying the promotions meet the CRSE standard. The reason is that health economic analyses are invariably based on clinical content. Extrapolations from intermediate end points with “substantial evidence” to long-term end points—even if analysts are transparent and rely on assumptions based on strong epidemiological evidence—trigger questions about violating Section 114 because they run afoul of the “directly-related to the approved indication” provision, and about whether they constitute health economic information.

In other cases, implied clinical claims may be more subtle as in the use of retrospective database analyses in which patients differ from those in the product’s RCT or indications. Trial patients meet strict criteria, whereas “real-world” patients reflect the vagaries of prescriber and patient behavior. Promotions involving retrospective database analysis could raise questions about whether they violate the “directly-related to the approved indication” clause. Retrospective database analyses of adherence could raise questions—despite adherence’s importance and the fact that it is difficult to study in trials—because superior adherence might imply a clinical claim about a drug that is not in the label.

However, one could also argue that, assuming that the CRSE standard is met, most of the cases would be allowable under a flexible definition of the “directly-related” clause. Under this interpretation, a company could extrapolate to dosages, populations, and settings as long as there are no off-label claims and analyses meet the CRSE criterion, which involves, as noted, conforming to best practices, such as prespecifying end points and the statistical analysis plan, using suitable statistical approaches, and conducting adequate sensitivity analyses.

The language of Section 114 is sufficiently vague that one might reasonably conclude that many of the case studies fall in a gray area, leaving legal, regulatory, health economics, and other teams within drug companies to interpret the statute and gauge the company’s risk tolerance. The seemingly limited use of Section 114 to date may reflect companies’ uncertainty about its scope. The dilemma is that payers are interested in knowing about real-world patients and comparative effectiveness research. The Patient-Centered Outcomes Research Institute was created to fund and disseminate such information. Drug companies, however, are hesitant to promote such information, even under Section 114, which was established to help companies engage health plans around real-world data to inform coverage and reimbursement.

The FDA is currently considering draft guidance on Section 114 [16]. To be sure, the agency faces important challenges in interpreting the statute and in regulating practices. As we have noted elsewhere, there remain concerns that allowing drug companies to promote information about end points that have not been adequately studied could still mislead intended audiences and remove incentives for companies to conduct randomized trials [1]. In addition, Section 114 has proven challenging to regulate and interpret. For example, definition and evaluation of the CRSE and relatedness criteria for any given submission are far from obvious.

At the very least, however, the case studies illustrate the need for clarity and flexibility. It would be useful if the agency defined what is meant by “formulary committee or other similar entity” (e.g., does it include a physician responsible for quality metrics in an ACO?). Clarity is also needed on what constitutes CRSE, and on when health economic claims violate the “directly-related” clause. The use of extrapolations from surrogate to longer-term end points within the context of a Section 114 claim is a particularly important issue that may warrant specific comment from the FDA. In our view, it would help if the FDA would permit flexibility around interpreting language of the statute in the context of promotions to payers, and a permissive attitude toward adherence claims and uses of real-world data, as long as studies are conducted according to best practice methodology (i.e., standards from Patient-Centered Outcomes Research Institute [5], ISPOR [4], and the Good Research for Comparative Effectiveness initiative [3]). Beyond that, as we have argued elsewhere [1], it would be even more helpful to broaden Section 114 to include clinical comparative effectiveness claims, a step that may require new legislation.

The case studies developed here have limitations. Most important, because of space constraints, they lack detail and context and are simplifications of reality. Judging whether a particular analysis reflects competent and reliable practices would require much more elaboration than is possible here. Still, we believe they illustrate the kinds of issues that drug companies and the FDA confront. They reveal challenges given the vague language of Section 114. The spirit of the law was to provide a protected space for communication between companies and plans about value. Ideally, such information can help payers make better formulary decisions and ultimately improve patient health for the resources expended. This article adds to the debate around the statute by presenting cases that illustrate the many potential uses of Section 114, and the section’s potential for providing an avenue for exchange between drug companies around health economics and value. The article also shows that in practice it is difficult to know exactly what the section allows given the imprecision of the statute and lack of guidance about its scope. Ideally, clarity and flexibility will be provided in FDA guidance and/or new legislation.

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R E F E R E N C E S