

# US FDA Modernization Act, Section 114

## Uses, Opportunities and Implications for Comparative Effectiveness Research

Peter J. Neumann,<sup>1</sup> Pei-Jung Lin<sup>1</sup> and Tom E. Hughes<sup>2</sup>

1 Center for the Evaluation of Value and Risk in Health, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, Massachusetts, USA

2 Market Access and Reimbursement, OptumInsight Life Sciences, Eden Prairie, Minnesota, USA

### Abstract

**Background:** Section 114 of the 1997 US FDA Modernization Act (FDAMA) is an important vehicle for pharmaceutical companies to promote the economic value of their drugs to formulary decision makers, but little is known about how the Section has been interpreted and used.

**Methods:** We conducted a web-based survey of a convenience sample of 35 outcomes directors of major pharmaceutical and biotechnology companies. We asked them about their interpretation of, and experiences with, Section 114, as well as their views regarding the FDA's role in the matter, and whether the advent of comparative effectiveness research (CER) will affect the use of Section 114 promotions.

**Results:** Of the 35 experts, 16 (46%) completed the survey. 81% stated they always or frequently consider using Section 114 when making promotional claims for drugs. 75% stated that the FDA should issue guidance on how to make such promotions to payers, especially what qualifies as "healthcare economic information" and "competent and reliable scientific evidence." Most expected to use Section 114 to a greater extent in the future, and agreed that the increased focus on CER would increase Section 114 use.

**Conclusions:** The survey suggests strong awareness about Section 114 among the outcomes directors and some use of the Section for promotional purposes. It also reflects a belief that CER will increase use of Section 114 promotions, and that guidance from the FDA is needed. More clarity – and, ideally, flexible interpretation – from the FDA is warranted, especially given the rise of CER.

### Background

The US FDA Modernization Act (FDAMA) of 1997 contains a provision, Section 114, stipulating the conditions under which drug companies

can promote health economic information to formulary decision makers. Since its enactment, FDAMA Section 114 has had a curious history. The FDA never issued guidance on the topic. Little has been written about it in the academic

literature. Although its intention was to provide drug companies flexibility in promoting economic messages about their products to health plans and similar organizations, the few observers who have commented on the matter have called attention to the restrictiveness of the Section.<sup>[1,2]</sup>

Yet Section 114 endures as a unique and potentially important vehicle for drug companies to promote information on the comparative economic value of their drugs. Moreover, the enactment of the US Patient Protection and Affordable Care Act (PPACA), which elevates the importance of comparative effectiveness research (CER), could breathe new life into Section 114.

Section 114 of the FDAMA states “Health care economic information provided to a formulary committee, or other similar entity, in the course of 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 ... if the health care economic information directly relates to an indication approved ... and is based on competent and reliable scientific evidence.”

The motivation for the Section was to provide drug companies greater flexibility to promote healthcare economic information (HCEI) [e.g. claims that a drug saves money or is cost effective]. Most notably, Section 114 amended the evidentiary standard for HCEI promotion from the prevailing “adequate and well-controlled trials” (commonly referred to as ‘substantial evidence’) to the new “competent and reliable scientific evidence.” Precisely what constitutes “competent and reliable scientific evidence” has never been formally defined or codified, although this phrase – used by the US Federal Trade Commission to judge the validity of promotional claims for certain other goods and services – suggests that evidence other than “substantial evidence” is permitted for HCEI promotion as long as the statute’s other provisions are satisfied.

Section 114 circumscribes the conditions for promotion of economic information. Such promotion must be “directly related” to the labelled indication, signifying limited manoeuvring room for interpreting the new competent and reliable standard. Presumably, promotion can include

‘costed-out’ clinical endpoints, which themselves have been studied in phase III trials (although only those that had made it into the label). For example, if a company receives an indication for fracture prevention for its new osteoporosis drug, Section 114 seems to permit the company to claim cost savings associated with fracture prevention, if the association between economic costs and fractures has a reasonable basis (and thus constitutes competent and reliable scientific information). On the other hand, the Section seems to prohibit use of economic models that extrapolate from surrogate clinical endpoints to longer-term clinical outcomes (e.g. from bone mineral density to fracture or mortality), if those long-term clinical outcomes are not supported by substantial evidence.

The Section also codified other limits, namely restricting promotion of HCEI to “formulary committees or similar entities” (thus barring promotion of HCEI under the “competent and reliable” standard to individual physicians or consumers). Any promotion of HCEI directly to physicians or consumers must adhere to the conventional “substantial evidence” provision, which generally means two adequate and well controlled clinical trials.

Because of the nebulous language of Section 114 and the lack of FDA guidance (and the lack of any legal mandate for guidance), little is known about how the Section has been interpreted and used. Even the FDA does not know, as they do not require companies to designate promotional materials submitted to the agency as Section 114 submissions<sup>[3]</sup> – and because they only scrutinize a small percentage of the promotional materials they receive. Research has shown that 10–20% of *print advertisements* on prescription drugs in major medical journals contain economic content – mostly the use of claims about market share, or the use of terms such as ‘price’, ‘cost’ and ‘savings’, although these are not Section 114 promotions, as they are targeted to individual physicians rather than to formulary decision makers.<sup>[4-6]</sup> The emergence of the Academy of Managed Care Pharmacy (AMCP) format and its use by US health plans as a vehicle for receiving information on the clinical and economic value of drugs has provided a

separate non-promotional channel for the exchange of HCEI between drug companies and health plans. Dossiers submitted under the AMCP format can contain economic models and off-label data, but the information can only be provided by drug companies in response to a health plan's "unsolicited request" and thus is non-promotional.

## Methods

To gain some understanding about use and perceptions of Section 114, we developed and disseminated an internet-based questionnaire to a sample of the US health outcomes directors in leading pharmaceutical and biotechnology companies. Specifically, we surveyed directors of health outcomes (or equivalent) departments at member companies of the Pharmaceutical Manufacturers Association (PhRMA)<sup>[7]</sup> and supplemented our search with outcomes directors at the top 11 biotechnology companies ranked by revenue,<sup>[8]</sup> who were not also members of PhRMA. We asked respondents about their interpretation of, and experiences with, Section 114, as well as their views regarding the FDA's role regarding the Act. Respondents were assured of anonymity and confidentiality. The survey stated that the research was being conducted independently by a non-profit academic research centre and that financial support was provided by a pharmaceutical company. Respondents were surveyed via SurveyMonkey.com, a web-based survey vendor. The survey required approximately 5–10 minutes to complete. No financial incentives were provided to respondents.

## Results

Of the 35 experts, 16 (46%) completed and returned the survey. All but one (94%) of the respondents reported being very familiar or familiar with Section 114 (table I). 81% stated that they always or frequently consider using Section 114 when making promotional claims for drugs. All reported having internal company legal and regulatory guidance on the creation, approval and use of Section 114 promotional claims.

Most respondents reported relatively infrequent use of Section 114. When asked about drugs for which they had evidence to support economic value, most respondents (56%) said they had created a Section 114 promotional piece in fewer than 50% of cases, and in those cases only one to two pieces per drug per year. Reasons for not using Section 114 included not feeling comfortable using the Section (25%); the fact that economic value information may not be included in the product label (13%); and uncertainty about whether creating a Section 114 piece was worth the benefit (13%).

Most respondents (63%) stated that their companies considered promotional economic information more valuable than AMCP dossier economic information. 75% said they expected to use Section 114 more in the future. Respondents mostly (75%) favoured FDA guidance on Section 114, particularly surrounding the definition of "competent and reliable scientific evidence." Two-thirds strongly agreed or agreed that the increased focus on CER and healthcare reform legislation would increase Section 114 use.

## Discussion

Since the enactment of FDAMA Section 114 in 1997, the landscape for evidence generation in the US has changed. The science of evidence syntheses has advanced. Observational databases to capture health and economic information have improved. There is greater use of real-world data for coverage and payment decisions.<sup>[9]</sup> Health plans have implemented more formal processes for considering evidence to inform formulary decisions.<sup>[10]</sup> And comparative effectiveness has taken centre stage.

Our survey suggests strong awareness about Section 114 among outcomes directors in pharmaceutical and biotechnology companies and some use of the Section for promotional purposes. It also suggests a need for FDA guidance.

The FDA has never issued guidance on Section 114 and is under no obligation to do so (i.e. sometimes Congress will mandate that an agency issue a report or guidance following passage of legislation and it did not do so in the case of Section 114). Furthermore, formal FDA guidance

**Table I.** Survey of outcomes directors in major pharmaceutical drug firms (n = 16)

Question	Survey response	%
<b>Use of Section 114</b>		
1. How familiar are you with FDAMA Section 114?	Familiar or very familiar	93.8
2. How often do you consider using Section 114 when making promotional claims?	Frequently or always	81.3
3. Does your company have internal legal/regulatory guidance on Section 114?	% saying yes	100
4. For what percent of your drugs that had evidence to support their economic value did you create a Section 114 promotional piece?	<50%	56.3
5. For drugs that had evidence to support their economic value, how many Section 114 pieces do you create per drug per year?	% saying 0–2 pieces	93.7
6. Why did you choose not to use Section 114?	Not feeling comfortable using Section 114	25.0
	Economic value information may not be included in the product label	12.5
	Not certain effort of creating a Section 114 piece was worth the benefit	12.5
7. What value does your company place on Section 114 promotion, compared to economic information contained in AMCP dossiers?	Promotional economic information is more valuable	62.5
	Equal in value	31.3
	Economic information in AMCP dossiers is more valuable	6.3
8. Did you expect to use Section 114 more often or less often in the future?	% saying more often	75.0
<b>Views on FDA guidance and comparative effectiveness research</b>		
9. Should the FDA issue guidance in this area?	% saying yes	75.0
10. If the FDA were to release guidance on Section 114, what area would be the most critical to address?	Competent and reliable scientific evidence	43.8
	Healthcare economic information	37.5
	Directly related to an approved indication	12.5
	Formulary committee or other similar entity	6.2
11. Do you agree or disagree that the increased focus on comparative effectiveness will increase the use Section 114 promotions?	% agree or strongly agree	68.8
12. Do you agree that US healthcare reform legislation will increase Section 114 use?	% agree or strongly agree	68.8

**AMCP** = Academy of Managed Care Pharmacy; **FDAMA** = US Food and Drug Administration Modernization Act.

could, in theory, hinder promotion of economic data in that the codification of rules could serve to restrict drug firms' manoeuvrability (in other words, with written guidelines, companies would be even more cautious in using the Section). However, three-quarters of our survey respondents supported FDA guidance on Section 114, particularly about what constitutes "competent and reliable" scientific evidence. Guidance for Section 114 may be particularly relevant given heightened attention to CER. Nearly 70% of respondents in our survey agreed that the increased focus on CER would increase use of Section 114 promotions.

The advent of CER invigorates a discussion about how existing regulatory and reimbursement bodies consider evidence. To date, much of

the CER evidence produced – and presumably much of the research that will be conducted or sponsored by the new Patient-Centered Outcomes Research Institute (PCORI) – would not achieve the "substantial evidence" requirements of the FDA for clinical claims. However, private and public payers, including the US Medicare programme will use such information for decision making.<sup>[11]</sup> This situation aggravates an existing imbalance: companies who want to disseminate CER are held to a higher standard than payers who wish to use it.<sup>[11]</sup> Moreover, one part of the US Government (FDA) uses an evidentiary standard different from another (Centers for Medicare and Medicaid Services). While the differences may be understandable given the agencies'

different missions and statutory authority, it does create a challenge for drug companies.

Section 114 offers a partial solution. It provides a communication channel for certain types of CER promotion (e.g. CER embodied in economic models or in economic analyses using observational data), and has the considerable advantage that it is based on existing law. It offers drug companies a potentially efficient way to disseminate promotional CER contained in economic information of interest to payers, especially in situations where a randomized controlled trial (RCT) is not feasible.<sup>[11]</sup>

Indeed, in some ways, Section 114 anticipated CER in the sense that it attempted to respond to the changing reimbursement landscape, recognizing the growing role of payers relative to individual physicians in decision making and the growing needs of health plans and other organized health decision makers for information about comparative value. The key question relates to the interpretation of the “competent and reliable” standard. A flexible reading of the statute could allow for greater promotion of CER-based economic analyses and models, assuming they are communicated only to health plans or similar entities.

The downside of a broad reading of the “competent and reliable” standard is that it could diminish incentives for companies to conduct certain types of RCTs (e.g. head-to-head trials not required for registration) in the first place.<sup>[12,13]</sup> The fear is that it could lead to widespread adoption of drugs before rigorous substantiating evidence is provided, and that formulary decision makers could be misled by economic superiority claims if they do not appreciate the type of evidence underlying claims of comparative clinical differences among products.<sup>[11]</sup>

On the other hand, incentives remain for companies to conduct active comparator RCTs so that they can use the information in promotion with payers, physicians and patients. In addition, Section 114 promotions are restricted to communications with health plans and similar groups, thus mitigating risks of individual physicians or consumers being misled. There is also evidence that plans are becoming savvier in judging evidence. Some large plans and pharmacy benefit

management companies (e.g. Wellpoint) are conducting outcomes studies in their own patient populations and using the information in formulary decisions, for example.<sup>[14]</sup> Certainly, payers have every incentive to develop their own expertise for judging economic models and CER.

## Conclusions

Outcomes directors in major pharmaceutical and biotechnology companies are considering and using FDAMA Section 114 when making promotional economic claims for drugs, despite their diverse interpretations of the law. Most believe that use of Section 114 promotions will increase in the future and that the focus on CER will increase the relevance of Section 114. Direction from the FDA may clarify how companies could share a range of CER with health plans. More dialogue with the FDA – and ideally a flexible interpretation of Section 114 that recognizes the growing demand from health plans for CER information – would be helpful for the field.

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Correspondence: Dr *Peter J. Neumann*, Director, Center for the Evaluation of Value and Risk in Health, Professor, Tufts University School of Medicine, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, 800 Washington St., Box #063, Boston, MA 02111, USA.  
E-mail: [pneumann@tuftsmedicalcenter.org](mailto:pneumann@tuftsmedicalcenter.org)