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Cures Act, FDA Draft Guidance Suggest Flexibility On Communication Of Real-World Drug Impacts, Though Questions Remain

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The debate about drug prices veils an intense discussion about the value that pharmaceuticals deliver. A key question pertains to the “real-world” impacts of prescription drugs, such as their potential to improve adherence, prevent hospitalizations, and reduce health costs.

The recently enacted 21st Century Cures Act contains a provision, “Section 3037: Health Care Economic Information,” designed to facilitate communication between pharmaceutical companies and formulary committees and payors about such real-world impacts. Section 3037 amends Section 114 of the Food and Drug Modernization Act of 1997 (FDAMA Section 114), which itself had sought to provide flexibility for drug companies to engage with formulary committees and like bodies about the potential value of their products. Notably, Section 114 had broadened the evidentiary standard for health care economic information (HCEI) communications from “substantial evidence” (typically two randomized controlled trials) to “competent and reliable scientific evidence,” as long as such claims were made to “formulary committees and similar entities” and “directly related to approved indications.”

In the wake of the Cures Act, the Food and Drug Administration (FDA) on January 17, 2017 issued long-awaited draft guidance entitled *Drug and Device Manufacturer Communications*

with Payors, Formulary Committees, and Similar Entities – Questions and Answers, which addresses key questions about the communication of HCEI by drug companies to formulary committees. This draft guidance provides the FDA's latest thinking on the topic, including the statutory changes of Section 3037.

FDAMA Section 114 had often been criticized because of its vague wording, and the lack of guidance from FDA about what constituted "competent and reliable scientific evidence." As we've noted previously, rather than providing a clear vehicle for the promotion of real-world data, Section 114 could have been (and was) interpreted by some to suggest broad limits on drug company promotion of most types of HCEI. For example, whether drug companies could promote a study based on analyses of real-world settings (e.g., analyses of patient-level observational databases) has been unclear because patients included in databases have not been randomized and because the patients differ from those included in drug registration trials.

Section 3037 and the new draft guidance offer the potential for more and better communications between drug companies and health plans, although they also raise questions and will require careful monitoring by regulators. The Section retains the "competent and reliable scientific evidence standard," but makes several key changes. Below we describe those changes, discuss the new FDA guidance, and address four important questions about how Section 3037 may be interpreted and implemented.

Section 3037 Of The Cures Act And The New FDA Draft Guidance On HCEI Communication

Clarifies The Definition Of Health Care Economic Information

Section 3037 states that HCEI means:

> any analysis (including the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis) that identifies, measures, or describes the economic consequences, which may be based on the separate or aggregated clinical consequences of the represented health outcomes, of the use of a drug. Such analysis may be comparative to the use of another drug, to another health care intervention, or to no intervention.

The inclusion in the definition of HCEI of terms such as "clinical data, inputs, clinical, or other assumptions" and "such analysis may be comparative" is potentially a far-reaching change. An inherent problem in Section 114 had stemmed from the fact that the Section was largely silent about what clinical content inside economic analyses was permissible (and that all economic analyses contain clinical assumptions and implications, explicit or implied). As a result, when communicating health economic information, drug companies always risked making clinical claims in violation of the statute. While that risk remains, it seems attenuated under Section 3037, perhaps to a considerable degree, because of explicit statements such as that HCEI includes the clinical input "underlying or comprising the analyses."

Changes 'Directly Relates To An Approved Indication' To 'Relates To An Approved Indication'

A second important statement in Section 3037 pertains to a provision of Section 114 that held that "health care economic information shall not be considered to be false or misleading

… if the health care economic information *directly* relates" to an approved indication for the drug (emphasis added). Section 3037 removes "directly" from the clause, making the test whether HCEI *relates* to an approved indication.

FDAMA Section 114 had always invited speculation about how far a company's health care economic analyses could vary from labeled claims. The provision seemed to prohibit extrapolations in health care economic analyses to claims about off-label indications, but questions had always remained about whether and to what extent companies could extrapolate over time and to populations, settings, or uses not explicitly covered by the label — the kinds of extrapolations that are integral to economic analyses. For example, analyses of real-world data will inevitably include patients and comparator treatments that differ, even if slightly, from those studied in randomized clinical trials, because it is impossible to match precisely patients in real-world databases to the detailed inclusion/exclusion conditions of trials.

In changing the term "directly relates" to "relates," the new law seems to allow companies more flexibility in making such extrapolations, both in real-world data analyses and in economic models. The new FDA draft guidance further supports this flexibility by providing examples of the types of information that may *relate* to an approved indication, including duration of therapy, practice setting, dosing, patient subgroups, length of hospital stay, validated surrogate endpoints, and clinical outcome assessments or other health outcome measures such as quality-adjusted life years (QALYs).

Requires A Disclaimer

Third, Section 3037 mandates that competent and reliable scientific evidence in economic analyses include, where applicable, "a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug." The provision is intended to alert audiences about the different evidentiary standards for HCEI as compared to clinical information. Presumably, such disclaimers would include, for example, a statement that analyses based on retrospective databases demonstrate associations and not causality, and that such analyses may not adjust well for possible confounders.

Clarifies The Audience For Health Care Economic Communications

Finally, Section 3037 amends Section 114's language about the intended recipients of health care economic communications, specifically from "a formulary committee or other similar entity" to "a payor, formulary committee, or other similar entity with knowledge and expertise in the area of health care economic analysis, carrying out its responsibilities for the selection of drugs for coverage or reimbursement."

The change thus broadens the audience covered to include payors, and clarifies that the intended recipients are those involved in coverage and reimbursement decisions. The FDA draft guidance adds that audiences also include "drug information centers, technology assessment panels, pharmacy benefit managers, and other multidisciplinary entities that review scientific and technology assessments to make drug selection, formulary management, and/or coverage and reimbursement decisions on a population basis for health care organizations."

Four Questions Going Forward

What Does 'Relates' To An Approved Indication Mean In Practice?

A first question is how much flexibility is provided by the phrase "relates" to the approved indication? In changing "directly relates" to "relates," Congress presumably intended to permit companies more latitude in communicating economic analyses beyond the narrow confines of the labeled indication.

The new FDA draft guidance, by providing examples of HCEI that would and would not be considered "related" to the approved indication, suggests that wide latitude would be allowed. According to the draft guidance, examples of HCEI considered "related" to the approved indication would include: duration of treatment; alternative practice settings; disease burden; dosing; patient subgroups; length of hospital stay; validated surrogate endpoints; and clinical outcome assessments or other health outcome measures. Examples of HCEI that would *not* be considered "related" to an approved indication include: an economic analysis of disease course modification for drugs only approved to treat disease symptoms; or an economic analysis of a patient population unrelated to the approved indication of the drug.

The FDA draft guidance seems an emphatic step toward permitting the communication of routine health economic information analyses, short of communications about unapproved uses claims. Section 114 had always raised questions, for example, about whether claims about a drug's impact on improved adherence or lowered hospitalization length of stay would be allowed, or whether a company could proactively communicate information using an economic model that extrapolated from surrogate to long-term endpoints. The new statute and guidance suggests that all of those types of claims would generally be permissible, as long as the information is based on competent and reliable scientific evidence and communicated to appropriate audiences. However, there will still be many questions about specific cases — when does an extrapolation from surrogate to long-term endpoints wander into territory of an off-label claim, for example? The details embedded in particular economic analyses will matter enormously.

Who Exactly Is The Intended Audience Of Section 3037 Communications?

Section 3037 clarifies that intended audiences for health economic analyses include "a payor…carrying out its responsibilities for the selection of drugs for coverage or reimbursement."

This is a welcome elucidation, though many observers had already considered payor audiences to be covered by the Section 114 language "formulary committees *and similar entities*." The Section 3037 change constitutes an overdue recognition of the new health care landscape in which payors, and not merely formulary committees, are involved in coverage and reimbursement decisions about prescription drugs. Notably, Section 3037 communications are still restricted to organizations (as opposed to practicing physicians or patients) that not only retain strong incentives to be informed and wary consumers of drug-company promotions, but who increasingly employ their own experts, and mine their own data.

Operationally, however, there remain practical questions about the scope of the audiences covered by Section 3037. Many practicing physicians working in integrated delivery networks, for example, now have income tied to quality metrics or are at-risk providers themselves; they thus function somewhat like payors involved in the selection of drugs in part for economic reasons, though they may not be involved in coverage and reimbursement decisions, per se. Are there circumstances in which such providers are covered by Section 3037 (e.g., if they are involved in helping the payor achieve quality metrics)? Moreover, in

practical terms, how do drug companies proactively communicate with physicians wearing multiple “hats”?

How Will FDA Regulate And Enforce Section 3037?

As was the case under Section 114, there will be many challenges for the FDA in interpreting the new statute and overseeing its implementation. In addition to issues noted above, a basic question looms about how the Agency will oversee Section 3037 communications given that analyses, such as those in economic models, may be shared by drug companies with payors but not published or printed.

What’s Next?

Whether the Cures Act and the new draft guidance will lead to more drug company communications around real-world impacts remains to be seen, though this would seem likely. The new Administration has stated generally that they will work to eliminate “red tape” at the FDA, which may embolden companies and lead FDA to take a relatively “hands-off” approach on the matter. Moreover, after the Cures Act was enacted in December, the Academy of Managed Care and Pharmacy (AMCP) praised Section 3037 as aligning with their recently developed recommendations on ways to clarify and expand Section 114.

Twenty years after FDAMA Section 114 was enacted, it is head spinning to have new legislation and draft guidance about the communication of HCEI arrive in the past two months. It will take some time to digest the meaning of the changes and to gauge their effects. But in the main they suggest considerable flexibility for drug companies to communicate proactively to payors and formulary committees about the real-world impacts of their products.

DRUGS AND MEDICAL INNOVATION

TAGS: 21ST CENTURY CURES ACT, FDAMA SECTION 114, FOOD AND DRUG MODERNIZATION ACT, HEALTH CARE ECONOMIC INFORMATION