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FDA Issues Draft Guidance on Payor Communications

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Shortly after the recently enacted, bipartisan 21st Century Cures Act, which revised and expanded the extent to which specific health care economic information (HCEI) may be disseminated to certain stakeholders, and comes within the context of the broader, ongoing discussion between FDA and stakeholders regarding promotion of medical products for unapproved uses (off-label communications), the US Food and Drug Administration (FDA) issued a draft guidance to address communication of HCEI by drug manufacturers to payors regarding FDA-approved drugs, and communications by drug and device manufacturers regarding investigational products.

In Depth

In the final days of the Obama administration, the US Food and Drug Administration (FDA) issued a draft guidance document titled *Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities – Questions and Answers* (Draft Guidance). The Draft Guidance comes shortly after the recently enacted, bipartisan 21st Century Cures Act (Pub. Law No. 144-255) (Cures Act), which revised and expanded the extent to which specific health care economic information (HCEI) may be disseminated to certain stakeholders, and comes within the context of the broader, ongoing discussion between FDA and stakeholders regarding promotion of medical products for unapproved uses (off-label communications).

The Draft Guidance addresses two topics: (1) communication of HCEI by drug manufacturers to payors regarding FDA-approved drugs, and (2) communications by drug and device manufacturers regarding investigational products.

Communication of HCEI by Drug Manufacturers to Payors Regarding FDA-Approved Drugs

HCEI is defined in 21 U.S.C. § 352(a) as “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 statute further provides that HCEI pertains to the economic consequences related to the clinical outcomes of treating a disease (or specific aspect of a disease) or of preventing or diagnosing a disease. The statute allows for the dissemination of HCEI to certain entities familiar with knowledge and expertise in health economic analyses, provided the HCEI is truthful and non-misleading, relates to an approved indication, and, if materially different from FDA-approved labeling (PI), is accompanied with a clear statement disclosing the differences from approved labeling. The Cures Act and Draft Guidance together broaden the ability of manufacturers to effectively engage in such communications.

Key provisions of the Draft Guidance include the following:

Potential recipients. The Cures Act expanded the list of entities to whom HCEI may be disseminated to expressly include communications to "payor[s], formulary committee[s], [and] other similar [entities] 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." Consistent with this approach, the Draft Guidance identifies 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" as potential recipients of HCEI. The Draft Guidance emphasizes that such entities must be part of a deliberative process and have the requisite knowledge and expertise to understand the HCEI and its limitations. This raises a question as to whether provider representatives or committees that make policy decisions on drug selection would meet this definition if the provider representatives also prescribe drugs. This is especially important with alternative payment models where providers take on risk and make policy decisions consistent with such risk.

Evidentiary support. During FDA's November 2016 public meeting, several stakeholders suggested what FDA should not limit HCEI to information that originates from well-controlled clinical studies. Potentially consistent with this approach, the FDA notes that HCEI should be based on "competent and reliable scientific evidence" (CARSE), which the agency defines as evidence developed using "generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results." This is generally consistent with the Federal Trade Commission's (FTC's) historical approach for reviewing scientific claims. The FTC's competent and reliable and scientific evidence standard focuses on transparency and methods consistent with experts in the field. In evaluating whether the amount and type of evidence meets the generally-accepted standards for such information, FDA will consider the current good research practices for substantiation established by authoritative bodies such as the International Society for Pharmacoeconomic Outcomes and Research (ISPOR) or the Patient-Centered Outcomes Research Institute (PCORI).

"Related to" an approved indication. To be considered "related to" an approved indication, HCEI analysis should relate to the disease or condition, manifestation of the disease or condition, or symptoms associated with the condition listed in the FDA-approved labeling. The Draft Guidance offers the following examples of types of HCEI analyses that "relate to" approved indications, several of which are consistent with recommendations made by industry and stakeholders following the original passage of section 114 of the Food and Drug Administration Modernization Act (FDAMA) in 1997:

- *Duration of Treatment*: where the FDA-approved indication does not limit duration of use, HCEI can incorporate information about long-term use that goes beyond the length of studies submitted as part of the FDA approval

- *Practice Setting*: HCEI analyses based on data from practice settings different from the settings of the clinical trials submitted as part of the product's FDA approval

- *Burden of Illness*: studies or data on broad management of a disease, including economic consequences of treatments on clinical outcomes (*e.g.*, impact on absent work days related to disease or illness)

- *Dosing*: studies on dosing regimen where it varies from FDA-approved labeling (*e.g.*, drug utilization data of actual patient use), provided such studies use approved dosage forms and strengths

- *Patient Subgroups*: studies or data on subgroups within the population indicated for use (*e.g.*, demographics, disease severity, comorbidities)

- *Length of Hospital Stay*: studies or data regarding treatment impact on length of hospital stay

- *Validated Surrogate Endpoints*: information where a surrogate endpoint is known to predict a clinical benefit

- *Clinical Outcome Assessments (COAs) or Other Health Outcome Measures (e.g., Quality Adjusted Life Year (QALY))*: when evaluated using valid and reliable measures (as determined by experts familiar with evaluating the merits of the particular health outcome measure) – in the case of QALYs, methods by which health status is captured and methods for valuation of health outcomes should be disclosed

- *Patient Persistence*: information on time from initiation to discontinuation of a treatment based on drug utilization data

- *Comparisons*: studies or comparison data against other drugs or treatments

The latter examples go beyond discussions following the original passage of section 114 of FDAMA and reflect a recognition of the acceptance of HCEI methods over time.

The Draft Guidance also clarifies that the following HCEI analyses are *not* considered to relate to an approved indication:

- Those analyses of disease course modification related to use of a drug that is approved only to treat the symptoms of a disease or condition only

- Those analyses derived from studies in patient populations not within the FDA-approved indicated patient population

Information to include when disseminating HCEI. When disseminating HCEI, a manufacturer should include appropriate background and contextual information necessary to allow payers to fully

understand the HCEI, including the following:

- *Study Design and Methodology*: study design and objectives as well as type of analysis, (*e.g.*, modeling technique, patient population and perspective or viewpoint of the economic analysis); treatment comparator; time horizon; outcome measures (including sources of clinical and non-clinical data); cost estimates (including source of cost data and date of pricing); and assumptions and rationales

- *Generalizability*: any factors which may limit the generalizability of the analysis should be disclosed

- *Limitations*: any limitations, including factors that can affect interpretability and reliability of the data such as limitations of the data sources, incomplete data, assumptions, choice of comparators and **exclusion of certain clinical outcomes**

- *Sensitivity Analysis*: uncertainties that could affect conclusions should be identified and a sensitivity analysis performed; HCEI should include adequate disclosures and rationales regarding the method used for the analysis, the variables chosen and the ranges for those variables

- *Additional Material for a "Balanced and Complete" Presentation*: a "conspicuous and prominent" statement describing any material differences from PI, a statement about the approved indication and a copy of the most current PI for the drug, risk information, disclosure of financial affiliation or biases (*e.g.,* study sponsorship, authorship, or significant financial interests) and **disclosure of omitted studies or data sources**. FDA recommends conducting a comprehensive literature search regarding the drug and an explanation of the methods used in this literature search and, if certain studies or data are omitted, an explanation and rationale as to why they were and how selective inclusion of data or studies may affect the conclusions

The Draft Guidance provides a non-exhaustive list of examples of the forms in which HCEI may be presented, including evidence dossiers, peer-reviewed journal publication reprints, budget-impact models or software packages comprising models with user manuals.

Finally, manufacturers should note that communicating HCEI is still considered "promotion" and is subject to various FDA submission requirements for promotional materials, *e.g.*, post-marketing requirements under 21 C.F.R. § 314.81(b)(3)(i) or various pre-dissemination requirements, as applicable. While the Draft Guidance may allow for expanded use of HCEI in a proactive rather than reactive (*i.e.*, responses to an unsolicited request) manner, it would also require a higher volume of materials to be submitted to FDA.

Communications by Drug and Device Manufacturers Regarding Investigational Products

Payors have long requested greater flexibility in communications regarding investigational products. As such, the Draft Guidance's provision of manufacturers with a clear framework for the dissemination of HCEI regarding investigational products is notable.

FDA explained that manufacturers can provide "factual, accurate, and non-misleading" information such as product information, information about the indication sought, factual results from studies,

anticipated timeline for FDA approval or clearance, targeting or marketing strategies and product-related programs or services regarding investigational products to the above-described entities.

The Draft Guidance emphasizes that such information should be accompanied with a statement that the product is still under investigation, that the safety or effectiveness has not yet been established and information about what stage of the development the product is in. The agency recommends that manufacturers update payors if or when previously provided information becomes outdated.

The Draft Guidance also explicitly states, however, that communications with health care providers or audiences broader than payors regarding unapproved uses remain prohibited.

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