Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities – Questions and Answers

Guidance for Industry and Review Staff

DRAFT GUIDANCE

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Guidance for Industry and Review Staff[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides answers to common questions regarding firms'[2] communication of health care economic information (HCEI) regarding their prescription drugs[3] to payors, formulary committees, or other similar entities[4] with knowledge and expertise in the area of health care economic analysis (collectively referred to as payors). This guidance also addresses common questions relating to dissemination of information about investigational drugs and devices[5] (medical products[6]) to payors before FDA approval or clearance of such products.

The questions and answers are grouped in the following categories:

[1] This guidance has been prepared by the Office of Prescription Drug Promotion in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Office of the Commissioner at the Food and Drug Administration.

[2] The term "firms" refers to medical product manufacturers, packers, and distributors and their representatives.

[3] Each biological product that also meets the definition of "drug" under the Federal Food, Drug, and Cosmetic Act (FD&C Act) is subject to provisions of the FD&C Act applicable to drugs, except that a biological product licensed under section 351 of the Public Health Service Act (PHS Act) is not required to have an approved new drug application under section 505 of the FD&C Act (21 U.S.C. 355). See section 351(j) of the PHS Act (42 U.S.C. 262(j)). For the purposes of this guidance, the term "drugs" means human prescription drugs, including those that are licensed as biological products.

[4] The terms "payors, formulary committees, or other similar entities" are discussed in Q.A.2/A.A.2 of this guidance.

[5] The term "device" refers to a medical device intended for human use, including a device that is licensed as a biological product.

[6] The term "medical products" refers to both drugs and devices.

- Communication of HCEI to payors regarding approved drugs
- Communications to payors about investigational drugs and devices (investigational products)[7]

This guidance describes FDA's current thinking on these topics.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A number of FDA's statutory and regulatory provisions potentially impact firms' communications with payors.[8] This guidance provides FDA's thinking on frequently asked questions regarding such communications in order to provide clarity for firms and payors.

[7] As used in this guidance, the term "investigational products" refers to drugs and devices that are not yet approved/cleared by FDA for any use (but which must be approved/cleared to be legally marketed), including products for which firms have submitted or plan to submit a new drug application (NDA), a biologics license application (BLA) (including an application submitted under the 351(k) pathway), an abbreviated new drug application (ANDA), a premarket approval application (PMA), a 510(k) submission, a *de novo* submission under section 513(f)(2) of the FD&C Act (21 U.S.C. 360c(f)(2)), or a Humanitarian Device Exemption (HDE) application.

[8] For example, section 502(a), as amended by section 114 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115) and section 3037 of the 21st Century Cures Act (Public Law 114-255), includes the following provision regarding communication of HCEI to payors about approved drugs:

> "Health care economic information provided 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, shall not be considered to be false or misleading under this paragraph if the health care economic information relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act [42 U.S.C. 262(a)] for such drug, is based on competent and reliable scientific evidence, and includes, where applicable, a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug under section 505 or under section 351 of the Public Health Service Act. The requirements set forth in section 505(a) or in subsections (a) and (k) of section 351 of the Public Health Service Act shall not apply to health care economic information provided to such a payor, committee or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary [of Health and Human Services] upon request …. For purposes of this paragraph, the term 'health care economic information' 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…. Such term does not include any analysis that relates only to an indication that is not approved under section 505 or under section 351 of the Public Health Service Act for such drug."

Specifically, section III.A provides FDA's thinking on frequently asked questions regarding communication of HCEI to payors about approved prescription drugs. Payors seek a range of information on effectiveness, safety, and cost-effectiveness of approved prescription drugs, including information from firms, to help support their drug selection, formulary management, and/or coverage and reimbursement decisions on a population basis. Often, this information differs from and can be provided in addition to the information FDA reviews in order to make approval decisions. Because coverage and reimbursement decisions by payors impact a large number of patients, FDA believes it is essential that information provided by firms to payors about their drugs be truthful and non-misleading.

Section III.B provides FDA's thinking on frequently asked questions regarding communications to payors about investigational products. Payors have also indicated that due in part to their need to, in some situations, plan for and make coverage and reimbursement decisions far in advance of the effective date of such decisions, they are also interested in receiving information from firms about medical products that are still under investigation or review by FDA. For the reasons described above, it is essential that information provided by firms about their investigational products be truthful and non-misleading.

III. QUESTIONS AND ANSWERS

A. Communication of HCEI by Firms to Payors Regarding Approved Drugs

Q. A.1. What is HCEI, and how can it be presented?

A. A.1. HCEI is defined in section 502(a) of the FD&C Act (21 U.S.C. 352(a)) (section 502(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."[9] 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.[10] HCEI may include comparative analyses of the economic consequences of a drug's clinical outcomes to alternative options (including the use of another drug) or to no intervention.

[9] See section 502(a), as amended by section 114 of the Food and Drug Administration Modernization Act of 1997 and section 3037 of the 21st Century Cures Act. As used in this guidance, the term "section 502(a)" refers to the part of that section specific to HCEI.

[10] Ibid. Section 502(a) further provides that HCEI provided to "a payor, formulary committee, or other similar entity" (payors) that "relates" to an approved indication and is based on "competent and reliable scientific evidence" will not be considered false or misleading. Those terms are discussed in Q.A.2/A.A.2, Q.A.4/A.A.4, and Q.A.5/A.A.5 of this guidance.

HCEI can be presented in a variety of ways that can include, but are not limited to, an evidence dossier, a reprint of a publication from a peer-reviewed journal, a software package comprising a model with user manual, or a budget-impact model.

Q. A.2. What is the appropriate scope of the audience for the communication of HCEI about approved drugs under section 502(a)?

A. A.2. Section 502(a) specifies that HCEI can be provided 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."[11]

This audience includes payors,[12] formulary committees[13] (e.g., pharmacy and therapeutics committees), 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.[14,15]

Such entities are constituted to consider HCEI (and other types of information) through a "deliberative process" and should have the appropriate range of "knowledge and expertise in the area of health care economic analysis" needed to interpret HCEI presented to them to inform their population-based decision-making process.[16,17] Expertise in this area is essential to understand and evaluate health care economic analyses and their limitations.

This guidance does not apply to dissemination of HCEI to other audiences, such as health care providers who are making individual patient prescribing decisions

[11] Ibid.

[12] The term "payors" refers to entities that are responsible for the financing or reimbursement of costs associated with health care services (e.g., third-party payers, health plan sponsors).

[13] The term "formulary committees" refers to multidisciplinary committees that have the responsibility for the selection of drugs and the management of a drug formulary.

[14] The term "health care organizations" may include entities such as integrated health care delivery networks, hospitals, and hospital systems.

[15] See page 65 of the House Report on Prescription Drug Use Reauthorization and Drug Regulatory Modernization Act of 1997 (H.R. 1411), H.R. Rep. No. 105-310. The report is available at https://www.congress.gov/congressional-report/105/house-report/310.

[16] Ibid.

[17] See section 502(a).

or consumers (e.g., dissemination via a public Web site). Dissemination of HCEI to these audiences is not covered by the recommendations of this guidance.[18]

Q. A.3. How does FDA intend to implement this guidance for HCEI disseminated in accordance with section 502(a)?

A. A.3. If a firm disseminates to an appropriate audience HCEI that is the type of information within the scope of section 502(a) (i.e., HCEI that relates to an approved indication and is based on competent and reliable scientific evidence (CARSE), as each of these elements is described in this guidance), FDA does not intend to consider such information false or misleading. HCEI should clearly and prominently present the information discussed in Q.A.7/A.A.7 and Q.A.8/A.A.8 in this section, including study design and methodology, generalizability, limitations, sensitivity analyses, and information relevant to providing a balanced and complete presentation. If HCEI includes material differences from the FDA-approved labeling, it must present "a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug,"[19] as discussed in Q.A.7/A.A.7.

In addition, FDA does not intend to use HCEI disseminated consistent with this guidance as providing evidence of a new intended use.

Q. A.4. Section 502(a) provides that HCEI shall not be considered false or misleading if, among other things, it "relates to an [approved] indication."[20] What types of information does FDA consider to relate to an approved indication?

A. A.4. To be considered related to an approved indication, HCEI analyses should relate to the disease or condition, manifestation of the disease or condition, or symptoms associated with the disease or condition in the patient population for which the drug is indicated in the FDA-approved labeling.

[18] The scope of the audience for HCEI is important because "it will ensure that the information is presented only to parties who have established procedures and skills to interpret the methods and limitations of economic studies. [Section 502(a)] is not intended to permit manufacturers to provide such health care economic information to medical practitioners who are making individual prescribing decisions nor is it intended to permit the provision of such information in the context of medical education." See page 65 of H.R. Rep. No. 105-310.

[19] See section 502(a).

[20] Section 502(a)(2)(B) of the FD&C Act also provides that the term HCEI "does not include any analysis that relates only to an indication that is not approved under section 505 or under section 351 of the Public Health Service Act." If an analysis is consistent with the recommendations in Q.A.4/A.A.4, FDA would consider it to be within the scope of HCEI as defined in section 502(a). On the other hand, if an analysis does not relate to an approved indication for a drug, as illustrated by the examples at the end of Q.A.4/A.A.4, FDA would not consider it to be within the scope of HCEI as defined in this section.

The table below provides examples of HCEI analyses that FDA believes could be considered related to an approved indication of a drug, despite incorporating information that does not appear within, and may vary in certain respects from, information presented in the FDA-approved labeling. These examples are for illustrative purposes only and are not intended to be comprehensive or restrictive.

Examples of HCEI Analyses That Relate to the Approved Indication

Example	Description
Duration of Treatment	Where the approved indication for a drug does not limit the duration of use, HCEI analyses may incorporate information about the long-term use of the drug for that indication over a period that is different from that addressed in the studies described in the FDA-approved labeling (e.g., if a drug is approved for a chronic condition with no limitation on its duration of use based on 24-week studies, economic consequences beyond 24 weeks can be modeled).
Practice Setting	HCEI analyses may be based on use of the drug for its approved indication in practice settings that differ from the settings of the clinical trials submitted to FDA in the application (e.g., results of clinical trials conducted in a fee-for-service setting could be extrapolated to a managed care or other setting).
Burden of Illness	HCEI analyses may be derived from studies of broad management of a disease for which the drug is indicated, including economic consequences of treatment on clinical outcomes (e.g., economic consequences of absent work days as a result of signs and symptoms associated with a disease).
Dosing	HCEI analyses may be based on data or studies of approved dosage forms and strengths of a drug for its approved indication, where the dosing regimen varies from the FDA-approved labeling (e.g., an observational study based on drug utilization data from a health plan database, where actual patient use of an approved dosage form and strength of a drug for an approved indication falls outside the recommended dosing regimen in the label, such as by taking at a different frequency or a different total dose than recommended).
Patient Subgroups	HCEI analyses may be derived from analyses of treatment effects in patient subgroups (e.g., demographics, disease severity, co-morbidities) that are

Example	Description
	within the patient population for the approved indication, even if these subgroup analyses were not pre-specified in the studies that formed the basis for approval of the drug.
Length of Hospital Stay	HCEI analyses may be derived from studies of treatment impacts on length of hospital stay.
Validated Surrogate Endpoints	HCEI analyses may be derived from clinical data demonstrating an effect on a surrogate endpoint that is known to predict clinical benefit (i.e., a validated surrogate endpoint).[21] For example, blood pressure reduction is a validated surrogate endpoint for reduction in certain cardiovascular events (e.g., stroke, myocardial infarction) pertaining to antihypertensive drugs (e.g., calcium channel blockers, angiotensin converting enzyme inhibitors).[22]
Clinical Outcome Assessments (COAs)[23] or Other Health Outcome Measures (e.g., Quality-Adjusted Life Year (QALY))[24]	HCEI analyses may be derived from studies involving the approved indication of a drug that assess COAs (e.g., patient-reported outcomes (PROs), such as compliance/adherence, work productivity, basic activities of daily living) or other health outcome measures (e.g., QALY) when they are evaluated using valid and reliable measures (as determined by experts who are familiar with evaluating the merits of a particular COA or other health outcome measure).

[21] See FDA's guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics.* We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance Web page at http://www.fda.gov/RegulatoryInformation/Guidances/. If there is insufficient evidence to demonstrate that a particular surrogate endpoint is capable of predicting clinical benefit, it generally should not be used as a basis for HCEI.

[22] See FDA's guidance for industry *Labeling for Outcome Claims for Drugs to Treat Hypertension*.

[23] A COA is any assessment of a patient's clinical state by the patient or a clinician. There are four types of COA measures (i.e., patient-reported outcomes, clinician-reported outcomes, observer-reported outcomes, and performance outcomes). See FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.*

[24] A QALY is a measure of the value of a health outcome that is typically scored on a scale from zero (corresponds to death) to one (corresponds to perfect or optimal health), integrating the life expectancy and treatment impact on morbidity of the compared interventions that may be used in HCEI.

Example	Description
Persistence[25]	HCEI analyses may be based on data estimating patient persistence on a drug for its approved indication (e.g., estimates based on drug utilization data from a health plan database).
Comparisons	HCEI analyses may be derived from studies comparing the safety or effectiveness of a drug for its approved indication to another drug or intervention or to no treatment.

The following are examples of HCEI analyses that are not considered to relate to an approved indication:

1. An economic analysis of disease course modification related to use of a drug that is approved only to treat the *symptoms* of the disease would not be considered related to the approved indication.[26] Thus, for example, if an analysis for a drug indicated for the *acute relief* of angina discussed the effect of the drug on delaying the *worsening of coronary artery disease* (disease course modification), FDA would not consider this to relate to the approved indication. Similarly, an analysis based on *prolonging patient survival* (disease course modification) for patients with heart failure would not be considered related to an indication for a drug approved only for the treatment of the *signs and symptoms* of heart failure.[27] As illustrated by these examples, if a drug is approved only to relieve the symptoms of a disease, HCEI analyses regarding use of the drug to prevent, cure, or mitigate/change the course of the disease would not be considered related to the drug's approved indication.

2. HCEI analyses derived from studies in patient populations that are not within the indicated patient population are not related to the approved indication of the drug. For example, an analysis regarding the treatment of cystic fibrosis (CF) in patients with *any* mutation in the CF gene would not be considered to relate to the approved indication for a drug approved to treat only *one specific* CF gene mutation.

[25] The term "persistence" refers to "the duration of time from initiation to discontinuation of therapy." See Cramer JA, Roy A, Burrell A, et al., Medication Compliance and Persistence: Terminology and Definitions, *Value Health*, 2008;11(1):44−47.

[26] See page 66 of H.R. Rep. No. 105-310.

[27] Ibid.

Q. A.5. What evidentiary support should firms have for their HCEI under section 502(a)?

A. A.5. Section 502(a) states that HCEI shall not be considered false or misleading if, among other things, it is "based on competent and reliable scientific evidence". FDA considers HCEI to be based on CARSE if the HCEI has been developed using generally-accepted scientific standards, appropriate for the information being conveyed, that yield accurate and reliable results. In evaluating whether the amount and type of evidence that forms the basis for a particular communication of HCEI meets the generally-accepted scientific standards for such information, FDA will consider the merits of existing current good research practices for substantiation developed by authoritative bodies (e.g., International Society for Pharmacoeconomic and Outcomes Research (ISPOR), Patient-Centered Outcomes Research Institute). For example, when evaluating HCEI based on indirect treatment comparisons in the absence of data from head-to-head controlled clinical trials, FDA may refer to guidelines issued by external expert bodies regarding current rigorous methodologies and best practices for such comparisons (e.g., network meta-analyses).

HCEI should clearly and prominently present the information discussed in Q.A.7/A.A.7 and Q.A.8/A.A.8 of this guidance, including study design and methodology, generalizability, limitations, sensitivity analyses, and information relevant to providing a balanced and complete presentation.

Q. A.6. Does the CARSE standard apply only to the economic components of HCEI, or does it also apply to the other components?

A. A.6. Under section 502(a), HCEI includes the clinical data, inputs, clinical or other assumptions, methods, results, and other components underlying or comprising the analysis of a drug's economic consequences. FDA considers the CARSE standard in section 502(a) to apply to all components of HCEI, including inputs and assumptions related to both economic consequences and clinical outcomes (i.e., safety and/or effectiveness). As discussed previously in Q.A.4/A.A.4, such information must also relate to an approved indication.

Q. A.7. What information should firms include when disseminating HCEI?

A. A.7. To enable payors to make informed coverage and reimbursement decisions and to help ensure that the information is not false or misleading under section 502(a), firms should include appropriate background and contextual information necessary to allow payors to fully understand the HCEI, including the elements discussed briefly below. This information, if applicable, should be presented clearly and prominently.

1. Study Design and Methodology

Firms should include an accurate overview of the design of the economic analysis, including a statement of the study objectives. For example, a clear description of the hypothesis tested should be provided and potential biases and/or confounders should be acknowledged. In addition, the following information about the study and/or methodology should be presented:

- **Type of Analysis:** The type of economic analysis selected (e.g., cost-minimization analysis, cost-effective analysis, cost-utility analysis, cost-benefit analysis, cost-consequence analysis) should be stated and the reason for its choice should be explained.[28]

Modeling: The type of modeling technique should be disclosed, with an explanation of the model choice, its scope, and its key variables/parameters.[29] The rationale and consequences of including and excluding specific variables in economic models should be discussed in the analysis.

Patient Population: Details about the patient population should be specified, including the number of patients and relevant demographic information, such as age, gender, ethnicity, clinical characteristics, and socioeconomic status.[30,31]

Perspective/Viewpoint: The perspective or viewpoint of the economic analysis should be clearly stated so that payors can understand the rationale for the selection of inputs (e.g., outcome measures, time periods, costs) and can, therefore, determine whether the HCEI is relevant to their particular health care organizations. Possible viewpoints can include those of the patient, employer, health care provider (e.g., clinician, institution), payor, regulatory body (e.g., government agency), or society (i.e., everyone impacted by the treatment).[32,33]

[28] Drummond MF, Jefferson TO, Guidelines for Authors and Peer Reviewers of Economic Submissions to BMJ, *BMJ*, 1996;313:(7052):275−283.

[29] Husereau D, Drummond M, Petrou S, et al., Consolidated Health Economic Evaluation Reporting Standards (CHEERS) − Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force, *Value Health*, 2013;16:231−250.

[30] Gold MR, Siegel JE, Russell LB, et. al., editors, Cost-Effectiveness in Health and Medicine, New York, NY: Oxford University Press, 1996.

[31] Husereau, et al., *op cit*.

[32] Gold, et al., *op cit*.

[33] Drummond, et al., *op. cit*.

- **Treatment Comparator:** The choice of comparator treatment (e.g., other drugs, other medical care, no treatment) should be fully explained.[34,35]

- **Time Horizon:** The choice of time horizon should be clearly stated and explained, including its relation to the major and relevant clinical outcomes (e.g., safety and effectiveness) and economic consequences related to the treatment of interest and its comparators.[36,37]

- **Outcome Measures:** The outcome measure(s) chosen should be fully described, as should the sources of clinical and/or nonclinical data. For example, clinical outcomes chosen could include PROs (e.g., compliance/adherence, work productivity, basic activities of daily living) or QALYs. Data sources may include clinical and nonclinical studies or other sources, such as administrative databases (e.g., health plan databases), electronic health records (EHRs), and registries.

- **Cost Estimates:** All of the relevant resource items for measurement and valuation for a treatment pathway in an economic analysis should be identified. Reference should be made to the source of cost data, including the date of the pricing.[38] In addition, full disclosure of and explanation for any data manipulations and methods (e.g., discount rates, adjustments for inflation, currency conversion) should be included.[39]

- **Assumptions:** A comprehensive listing of all assumptions (clinical and nonclinical) and associated rationales should be made explicit in the explanation of the methodology for the economic analysis.[40] Assumptions may include, for example, information related to patient demographics or characteristics, natural disease course, disease management/clinical practice, and cost of clinical events. All evidence to support assumptions made should be provided.

[34] Gold, et al., *op. cit*.

[35] Husereau, et al., *op. cit*.

[36] Gold, et al., *op. cit*.

[37] Husereau, et al., *op. cit*.

[38] Ibid.

[39] Ibid.

[40] Ibid.

283 *2. Generalizability*
284
285 Generalizability refers to the applicability of HCEI obtained in one health care
286 setting or patient population to another. Any factors which may limit the
287 generalizability of the economic analysis should be disclosed.[41]
288
289 *3. Limitations*
290
291 A discussion of the limitations of the economic analysis should be made
292 explicit.[42] Factors that may affect the interpretability and reliability of an
293 economic analysis include, but are not limited to, limitations of the study design,[43]
294 limitations of the data sources, incomplete data, assumptions made, choice of
295 comparators, and exclusion of certain clinical outcomes. For example, regarding
296 study design, limitations and methodological issues associated with observational
297 studies[44] and indirect treatment comparisons[45] should be fully described, as they
298 may inform conclusions that can be reliably made based on these analyses.
299
300 *4. Sensitivity Analysis*
301
302 Uncertainty may arise from data sources, extrapolation, or analytical methods
303 employed in an economic analysis. Therefore, uncertainties that could affect the
304 conclusions in HCEI should be identified, and a sensitivity analysis should be
305 performed. HCEI should include adequate disclosures and rationales regarding
306 the method used for the sensitivity analysis, the variables chosen, and the ranges
307 for those variables.[46]
308
309 *5. Additional Material Information for a Balanced and Complete Presentation*
310

[41] Siegel JE, Weinstein MC, Russell LB, et al., Recommendations for Reporting Cost-Effectiveness Analyses, Panel on Cost Effectiveness in Health and Medicine, *JAMA*, 1996;276(16):1339−1341.

[42] Gold, et al., *op. cit*.

[43] Regarding study design limitations, firms should disclose whether the study lacked randomization, blinding, or a control group; lacked assay sensitivity; failed to include pre-specified endpoints; failed to include endpoints that are valid and reliable measures of the outcomes of interest; failed to identify dosing, patient population, patient drop outs, selection and timing of endpoints; failed to meet the primary endpoint; etc.

[44] Berger ML, Martin BC, Husereau D, et al., A Questionnaire to Assess the Relevance and Credibility of Observational Studies to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report, *Value Health*, 2014;17(2):143−156.

[45] Song F, Loke YK, Walsh T, et al., Methodological Problems in the Use of Indirect Comparisons for Evaluating Healthcare Interventions: Survey of Published Systemic Reviews, *BMJ*, 2009;338:b1147.

[46] Husereau, et al., *op. cit*.

A balanced and complete presentation includes material information such as the following:

- **Conspicuous and Prominent Statement Describing Material Differences:** If HCEI includes material differences from the FDA-approved labeling, including assumptions that vary in certain respects from the information presented in the FDA-approved labeling, "a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug"[47] must be presented.

  Furthermore, firms should not misleadingly represent that the clinical assumptions that vary from the FDA-approved labeling have been found by FDA to be safe and effective.

- **FDA-Approved Indication/FDA-Approved Labeling:** HCEI should include a statement regarding the FDA-approved indication of the drug and be accompanied by the most current FDA-approved labeling.

- **Disclosure of Omitted Studies or Data Sources**: As a general matter, the presentation of HCEI would not be considered to be balanced and complete if relevant data or information is available but was not considered and included in the analysis. This is especially true if the omitted data or information is from rigorous studies (e.g., adequate and well-controlled trials). It is, therefore, recommended that firms perform a comprehensive literature search and that their HCEI include an explanation of the methods used in the literature search (e.g., databases or sources used, time period covered, and criteria/keywords used to search the databases and sources and to determine what data or information to include/exclude). If HCEI is created without using all available relevant data, HCEI should clearly explain that certain studies or data sources were omitted from the analysis, the reasons they were not included, and how such a selective inclusion of studies or data sources may change or affect the conclusions.

- **Risk Information:** HCEI should disclose important risk information associated with the approved use of the drug and, under section 502(a), must disclose any additional risk information related to clinical assumptions in economic analyses that vary from the FDA-approved labeling (e.g., risks observed in a particular patient subgroup).

[47] See section 502(a). Factors that can influence the conspicuous and prominent presentation of a statement include, but are not limited to, the location of the statement; the font size and style of the statement text; the contrast between text and background; and the white space between and around text.

- **Financial/Affiliation Biases:** HCEI should disclose potential financial or affiliation biases, such as the disseminating firm's role in funding underlying research or in drafting underlying publications or presentations or the names of any authors of studies or analyses who received compensation from the firm or who had a significant financial interest in the firm, to the extent reasonably known by the firm at the time of dissemination.

Q. A.8. If HCEI is based on COAs or other health outcome measures, are there any additional considerations of which firms should be aware?

A. A.8. When HCEI includes COAs (e.g., PROs, including compliance/adherence, work productivity, basic activities of daily living) or other measures of health outcomes (e.g., QALYs), information regarding the validity and reliability of the measures used in assessments of the COA (as determined by experts familiar with evaluating the merits of a particular COA)[48] or the health outcome measure should be included.

Regarding health outcome measures such as QALYs, the following should be considered to facilitate interpretability and comprehensibility of the information: (1) the methods by which the patient's health status is captured should be disclosed, and the rationale for the health status measures included in the analysis (e.g., physical function, psychological function, social function, impairment, pain) should be provided and (2) the methods for the valuation of health outcomes should be disclosed, and their appropriateness for the patient population and the disease or condition being studied should be explained.

Q. A.9. Is HCEI for prescription drugs disseminated in accordance with section 502(a) considered to be promotion? Do FDA's requirements for promotional materials apply to HCEI?

A. A.9. HCEI disseminated in accordance with section 502(a) is promotion, and, therefore, is subject to FDA's requirements for submission of promotional materials. These include, but are not limited to, the post-marketing requirement at 21 CFR 314.81(b)(3)(i) to submit such materials to FDA at the time of initial publication or dissemination (using Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use)) and, for HCEI about drugs submitted for approval under the accelerated approval pathway or about drugs approved based on animal studies,[49] the requirements regarding pre-dissemination submission of promotional materials.

[48] For further guidance regarding characteristics of valid and reliable assessments of COAs, please see FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.*

[49] See 21 CFR 314.550, 314.640, 601.45, and 601.94.

All supporting information for HCEI should be referenced and be made available upon request.[50]

Q. A.10. What are the Agency's policies for communication of HCEI regarding unapproved uses of approved drugs?

A. A.10. FDA has issued a draft guidance describing our thinking on how firms can respond to unsolicited requests, including requests from payors, for unapproved use information related to their FDA-approved prescription drugs and FDA-approved or cleared medical devices.[51] In addition, FDA has provided separate guidances describing recommended practices for the dissemination by firms of scientific and medical publications discussing unapproved uses of approved drugs or approved or cleared medical devices.[52,53]

Q. A.11. What are the Agency's policies regarding risk-sharing and other value-based contracts between firms and payors?

A. A.11. This guidance addresses the communication of HCEI to payors, which may include communication of HCEI in the course of discussions between firms and payors related to risk-sharing and other value-based contracts. This guidance, however, is not intended to address the terms of contracts between firms and payors. FDA does not regulate the terms of contracts between firms and payors.

B. Communications by Firms to Payors Regarding Investigational Drugs and Devices

Medical product firms may wish to provide certain types of information to payors regarding their investigational products. Such information may help payors plan and budget for future coverage and/or reimbursement decisions prior to FDA approval or clearance of investigational products. This section provides answers to frequently asked questions on this topic.

[50] In addition, under section 502(a), if FDA requests submission of information that is relevant to the substantiation of HCEI, firms are required to provide FDA such information, which may include the primary data and analysis methods used to support the HCEI.

[51] FDA's draft guidance *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*.

[52] FDA's guidance *Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices* (January 2009), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm125126.htm.

[53] FDA's revised draft guidance *Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices* (February 2014).

Q. B.1. What are the types of information covered by this section of the draft guidance and what is FDA's approach with respect to firms that wish to provide such information prior to FDA approval or clearance of an investigational product?

A. B.1. FDA does not intend to object, under 21 CFR 312.7(a) or 21 CFR 812.7(a) or otherwise, to the following types of information about investigational products (as defined in this guidance) provided by firms to payors prior to FDA approval or clearance, that is unbiased, factual, accurate, and non-misleading **and** when presented with information discussed in Q.B.2/A.B.2:

- Product information (e.g., drug class, device design)
- Information about the indication sought, such as information from the clinical study protocol(s) about endpoint(s) being studied and the patient population under investigation (e.g., number of subjects enrolled, subject enrollment criteria, subject demographics)
- Factual presentations of results from clinical or preclinical studies (i.e., no characterizations or conclusions should be made regarding the safety or effectiveness of the product)
- Anticipated timeline for possible FDA approval/clearance
- Product pricing information
- Targeting/marketing strategies (e.g., outreach activities planned to generate prescriber awareness about the product)
- Product-related programs or services (e.g., patient support programs)

Q.B.2. What other information should firms provide to payors when communicating information about their investigational products?

A. B.2. FDA recommends that firms provide the following information to payors when communicating information about investigational products:

- A clear statement that the product is under investigation and that the safety or effectiveness of the product has not been established
- Information related to the stage of product development (e.g., the phase of clinical trial in which a product is being studied and how it relates to the overall product development plan)

FDA also suggests that firms provide follow-up information to payors if previously communicated information becomes outdated as a result of significant changes or as a result of new information regarding the product (e.g., failure to

meet primary effectiveness endpoint in the phase 3 trial) or its review status (e.g., an application is determined to not be ready for approval upon completion of the review cycle, a study is placed on a clinical hold).

Q. B.3. ***What types of information would be considered <u>inappropriate</u> to communicate to payors about investigational products?***

A. B.3. Communications between firms and payors that represent that an investigational product is FDA-approved/cleared or otherwise safe or effective for the purpose(s) for which it is under investigation would not be appropriate.