
Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities Questions and Answers Guidance for Industry and Review Staff

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Office of the Commissioner (OC)**

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Guidance for Industry and Review Staff

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This guidance represents 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 office 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)³ regarding their prescription *drugs*⁴ and medical *devices*⁵ to payors, formulary committees, or other similar entities⁶ 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 to payors of information about *medical products*⁷ that are not yet approved or cleared for any use and dissemination to payors of information about unapproved uses of approved/cleared medical products.

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, including representatives of these entities.

³ See Q.A.1/A.A.1 for a definition of HCEI.

⁴ 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.

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 terms “payors, formulary committees, or other similar entities” are discussed in Q.A.2/A.A.2 of this guidance.

⁷ The term “medical products” refers to both drugs and devices.

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The questions and answers are grouped in the following categories:

- Communications of HCEI to payors regarding approved drugs;
- Communications of HCEI to payors regarding approved/cleared devices;⁸
- Communications to payors about unapproved drugs/devices (*unapproved products*⁹); and about unapproved uses of approved/cleared medical products.

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.¹⁰ This guidance provides FDA’s thinking on frequently asked questions regarding such communications in order to provide clarity to firms and payors.

⁸ As used in this guidance, the term “approved/cleared device,” and similar terms, includes devices that are legally on the market as a result of premarket approval, 510(k) clearance, De Novo marketing authorization, a humanitarian device exemption (HDE) approval, or an exemption from premarket notification.

⁹ As used in this guidance, the term “unapproved 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 HDE application.

¹⁰ For example, section 502(a) of the FD&C Act, (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

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Payors are a sophisticated audience with a range of expertise in multiple disciplines, as well as established procedures for carefully considering evidence about medical products. Generally, payors possess financial resources and motivation to closely scrutinize information about medical products as part of their decision-making process, including an evaluation of the limitations and reliability of that information. Payors seek a range of information on effectiveness, safety, and cost-effectiveness of approved/cleared medical products, including information from firms, to help support their product 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 making approval/clearance decisions.

Because coverage and reimbursement decisions by payors impact many patients, FDA believes it is critical that information provided by firms to payors about their medical products be truthful and non-misleading and that appropriate background and contextual information be provided to enable payors to make informed decisions. This guidance provides FDA’s recommendations for firms to help them ensure that their communication of HCEI to payors about approved/cleared medical products is truthful and non-misleading. Specifically, section III.A provides FDA’s thinking on frequently asked questions regarding communication of HCEI to payors about approved prescription drugs under section 502(a) of the FD&C Act (21 U.S.C. 352(a)). Section III.B provides FDA’s thinking on frequently asked questions regarding communication of HCEI to payors about approved/cleared devices. As noted in section III.B, although the language in section 502(a) addressing HCEI applies only to drugs, the general requirement in section 502(a) that labeling not be false or misleading applies to devices as well as to drugs. FDA considers firms’ communications of HCEI to payors that otherwise meet the definition in section 201(m) of the FD&C Act (21 U.S.C. 321(m)) to be labeling.¹¹ Thus, FDA believes the recommendations

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.”

¹¹ The first sentence of section 502(a)(1) of the FD&C Act provides that a drug or device is deemed to be misbranded “[i]f its labeling is false or misleading in any particular.” Under longstanding FDA practice and FDA’s statute, regulations, and case law, “labeling” encompasses more than merely the label of the drug, but extends to other written, printed, or graphic matter “accompanying such article” (section 201(m) of the FD&C Act; see also 21 CFR 1.3(a)). According to *Kordel v. United States*, 335 U.S. 345, 350 (1948), the language “accompanying such article” in the labeling definition in the FD&C Act includes materials that supplement or explain an article, “[n]o physical attachment one to the other is necessary. It is the textual relationship that is significant.” When Congress first amended section 502(a) to include a provision about communication of HCEI, it indicated this provision established that health care economic information “may be included in . . . labeling or advertising submitted to a formulary committee, managed care organization, or similar entity” (see pages 87-88 of the Senate Report on the Food and Drug Administration Modernization and Accountability Act of 1997 (S. 830), S. Rep. No. 105-43, available at <https://www.congress.gov/congressional-report/105th-congress/senate-report/43/1>), and that under “FDA’s current postmarketing reporting regulations, health care economic information as defined in this section

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provided in section III.A are generally applicable to firms' communication of HCEI to payors about devices as well, and can help ensure these communications are not false or misleading.

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 not yet approved/cleared by FDA for any use, and about unapproved uses of approved/cleared medical products. For the reasons described previously, it is critical that information provided by firms about their unapproved products and about unapproved uses of approved/cleared products be truthful and non-misleading. Section III.C provides FDA's thinking on frequently asked questions regarding communications to payors about unapproved products and about unapproved uses of approved/cleared products.

III. QUESTIONS AND ANSWERS

A. Communications 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) 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.”¹² HCEI pertains to the economic consequences (including, but not limited to, monetary costs or resource utilization) related to the clinical outcomes of treating a disease (or specific aspect of a disease) or of preventing or diagnosing a disease.¹³ HCEI may include

must be submitted to the FDA at the time it is initially provided to a formulary committee or other similar entity” (see page 67 of the House Report on the Prescription Drug User Fee Reauthorization and Drug Regulatory Modernization Act of 1997 (H.R. 1411), H.R. Rep. No. 105-310, available at <https://www.congress.gov/congressional-report/105/house-report/310>). The referenced postmarketing reporting requirements apply to promotional labeling (as well as to advertisements) (see 21 CFR 314.81(b)(3)(i)). Since Congress sought to address the use of HCEI in the context of these promotional materials, and firms have disseminated this information through promotional labeling materials, FDA's longstanding approach has been to consider communication of HCEI about drugs under this section to be promotional labeling. See also Q.A.9/A.A.9. The Agency similarly considers communications of HCEI about devices to be promotional labeling.

¹² See section 502(a), as amended by section 114 of FDAMA 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.

¹³ See footnote 12. 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” shall 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.

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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.

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 a user manual, a budget-impact model, a slide presentation, or a payor brochure.

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.”¹⁴

This audience includes public and private sector payors,¹⁵ formulary committees¹⁶ (e.g., pharmacy and therapeutics committees), drug information centers, technology assessment committees, pharmacy benefit managers, third party administrators, and other multidisciplinary entities that, on behalf of health care organizations,¹⁷ review scientific and/or technology assessments to make drug or device selection or acquisition, formulary management, and/or coverage and reimbursement decisions on a population basis.¹⁸

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.^{19,20} Expertise in this area is critical to understand and evaluate health care economic analyses and their limitations.

¹⁴ See footnote 13.

¹⁵ The term “payors” refers to entities who are responsible for the financing or reimbursement of costs associated with health care services (e.g., third-party payors, health plan sponsors, state Medicaid programs).

¹⁶ The term “formulary committees” refers to multidisciplinary committees that have the responsibility for the selection of drugs and the management of a drug formulary.

¹⁷ The term “health care organizations” may include entities such as integrated health care delivery networks, hospitals, and hospital systems.

¹⁸ See page 65 of H.R. Rep. No. 105-310.

¹⁹ See footnote 18.

²⁰ See section 502(a).

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Because section 502(a) provides for communication of HCEI only to particular audiences, dissemination of HCEI to other audiences is not covered by the recommendations of this guidance.²¹ Thus, this guidance does not apply to dissemination of HCEI to other audiences, such as health care providers who are making individual patient prescribing decisions or consumers (e.g., dissemination directed toward prescribers or consumers via a public website). This is not meant to suggest that individuals who have multiple roles, such as a health care professional who serves on a formulary committee and also provides care for individual patients, would not fall within the scope of the appropriate audience for this guidance when they are carrying out their professional responsibilities for selection of drugs for coverage or reimbursement for a payor, formulary committee, or similar entity.

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 of 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 (e.g., new or increased risks, different dosing/use regimens, different endpoints, more-limited/targeted patient populations), 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,”²² as discussed in Q.A.7/A.A.7.

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

²¹ Congress believed that limiting 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.

²² See section 502(a).

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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.”²³ 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, the 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.

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 an 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).
Health Care Setting	HCEI analyses may be based on use of the drug for its approved indication in health care settings that differ from the settings of the clinical trials submitted to FDA in the application (e.g., results of clinical trials conducted only in a fee-for-service setting could be extrapolated to a managed care or

²³ 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). If an analysis is based on data that includes both patients who are within the indicated patient population and patients who are outside of the indicated patient population (e.g., a drug is approved to treat condition X in adults and a data source used for an analysis only can provide aggregate information for all patients who are using the drug to treat condition X, including pediatric patients), FDA would also consider that to be within the scope of HCEI as defined in section 502(a). On the other hand, if an analysis does not relate at all 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.

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Example	Description
	other setting, or results of clinical trials conducted in a hospital center could be extrapolated to an ambulatory care setting).
Burden of Illness	HCEI analyses may be derived from studies of the burden of a disease for which the drug is indicated, including economic consequences of the effect the treatment has on clinical outcomes (e.g., economic consequences of absent work days as a result of signs and symptoms associated with a disease).
Dosing/Use Regimen	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/use regimen varies from the FDA-approved labeling (e.g., an observational study based on real-world drug utilization data from a health plan database or the electronic health records of a hospital system), where actual patient use of an approved dosage form and strength of a drug for an approved indication falls outside the recommended dosing/use 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), including subgroups with response rates that may vary from the rates reflected in the FDA-approved labeling, that are 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.
Surrogate or Intermediate 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) or on a surrogate or intermediate clinical endpoint that is

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Example	Description
	reasonably likely to predict clinical benefit. ²⁴
Clinical Outcome Assessments (COAs)²⁵ or Other Health Outcome Measures (e.g., Quality-Adjusted Life Year (QALY))²⁶	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 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).
Compliance/Adherence²⁷	HCEI analyses may be derived from studies assessing patient compliance/adherence with a drug for its approved indication.
Persistence²⁸	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

²⁴ For more information on surrogate and intermediate clinical endpoints, see FDA’s guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics*, and, for devices, see FDA’s guidance for industry, tool developers, and Food and Drug Administration staff *Qualification of Medical Device Development Tools*. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

²⁵ 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*.

²⁶ 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.

²⁷ The terms “compliance” and “adherence” refer to “the extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen.” See Cramer JA, Roy A, Burrell A, et al., Medication Compliance and Persistence: Terminology and Definitions, *Value in Health*, 2008;11(1):44-47.

²⁸ The term “persistence” refers to “the duration of time from initiation to discontinuation of therapy.” See footnote 27.

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Example	Description
	intervention or to no treatment.

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

- 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.²⁹ Thus, for example, if an analysis for a drug indicated for the management of pain in cancer patients discussed the effect of the drug on delaying the progression of cancer or on prolonging patient survival (disease course modification), FDA would not consider this to relate to the approved indication.
- HCEI analyses derived from studies limited to patient populations that are not within the indicated patient population are not related to the approved indication of the drug. For example, if a drug is approved only for use in patients in a certain age group, an analysis regarding the treatment of only patients outside of that age group would not be considered to relate to the approved indication for the drug.

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 existing current good research practices for substantiation developed by authoritative bodies (examples of such bodies include, but are not limited to, International Society for Pharmacoeconomic and Outcomes Research (ISPOR), International Society for Pharmacoepidemiology (ISPE), Patient-Centered Outcomes Research Institute (PCORI), and Agency for Healthcare Research and Quality (AHRQ)). For example, when evaluating HCEI based on indirect treatment comparisons in the absence of data from head-to-head

²⁹ See generally section 502(a)(1) and (a)(2)(B) of the FD&C Act. As a clinical matter, a drug that is approved only to relieve symptoms of a disease cannot be assumed to prevent, cure or change the course of the disease; therefore, assumptions about the health care economic consequences of use of such a product for preventing, curing, or changing the course of the disease would not be considered to relate to the product’s approved indication. See also page 66 of H.R. Rep. No. 105-310 for additional discussion.

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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 applicable 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 in order to fall within the provisions of section 502(a) regarding HCEI.

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

A.A.7. To enable payors to make informed coverage and reimbursement decisions, firms should include appropriate background and contextual information when disseminating HCEI. Included below are examples of the types of background and contextual information that may be material to HCEI presentations; some of these categories of information may not be applicable to particular HCEI presentations. This information, where relevant, should be presented clearly and prominently. The disclosure of the pertinent information can be concise so long as all material information (such as the source(s) of data used, the outcome measures used, the type of analysis, the limitations of the analysis, and the generalizability of the findings) is provided, as further described below. FDA recommends that this contextual information be presented in conjunction with the information within the HCEI presentation to which it relates or that the HCEI presentation include a prominent reference to where the information can be found within the presentation.

FDA is aware that some authoritative bodies have developed format recommendations for firms' communications to payors, which include recommendations for where firms should disclose the information described below within their communications. The recommendations provided here are not meant to suggest that firms should make duplicative disclosures of this background/contextual information if it is already provided in accordance with such format recommendations.

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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 where relevant:

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, budget impact analysis) should be stated, and the reason for its choice should be explained.³⁰

Modeling: The type of modeling technique should be disclosed, with an explanation of the model choice, its scope, and its key variables/parameters.³¹ 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, sex, race, clinical characteristics, and socioeconomic status.^{32,33}

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).^{34,35}

Comparator: The choice of comparator (e.g., other drugs, other medical care, no treatment) should be explained.^{36,37}

³⁰ Drummond MF, Jefferson TO, Guidelines for Authors and Peer Reviewers of Economic Submissions to the BMJ, *BMJ*, 1996;313:(7052):275-283.

³¹ 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 in Health*, 2013;16:231-250.

³² Gold MR, Siegel JE, Russell LB, et. al., editors, *Cost-Effectiveness in Health and Medicine*, New York, NY: Oxford University Press, 1996.

³³ See footnote 31.

³⁴ See footnote 32.

³⁵ See footnote 30.

³⁶ See footnote 32.

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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.^{38,39}

Outcome Measures: The outcome measure(s) chosen should be described, as should the sources of clinical and/or nonclinical data. For example, clinical outcomes chosen could include PROs (e.g., work productivity, basic activities of daily living) or QALYs. Data sources may include clinical and nonclinical studies or other sources, such as real-world data from 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.⁴⁰ In addition, disclosure of and explanation for any data manipulations and methods (e.g., discount rates, adjustments for inflation, currency conversion) should be included.⁴¹

Assumptions: A listing of all assumptions (clinical and nonclinical) and associated rationales should be made explicit in the explanation of the methodology for the economic analysis.⁴² Assumptions may include, for example, information related to patient demographics or characteristics, natural disease course, disease management/clinical practice, and cost of clinical events. A list of references for the evidence used to support assumptions made should be provided. Copies of the references should be provided to payors upon request.

2. *Generalizability*

Generalizability refers to the applicability of HCEI obtained in one health care setting or patient population to another. Any factors that may limit the generalizability of the economic analysis should be disclosed.⁴³

³⁷ See footnote 31.

³⁸ See footnote 32.

³⁹ See footnote 31.

⁴⁰ See footnote 31.

⁴¹ See footnote 31.

⁴² See footnote 31.

⁴³ 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.

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3. *Limitations*

A discussion of the limitations of the economic analysis should be made explicit.⁴⁴ Factors that may affect the interpretability and reliability of an economic analysis include, but are not limited to, limitations of the study design and methodology.⁴⁵ For example, limitations and methodological issues associated with observational studies⁴⁶ and indirect treatment comparisons⁴⁷ should be described as they may inform conclusions that can be reliably made based on these analyses.

4. *Sensitivity Analysis*

Uncertainty may arise from data sources, extrapolation, or analytical methods employed in an economic analysis. Therefore, uncertainties that could affect the conclusions in HCEI should be identified, and a sensitivity analysis should be performed. HCEI should include adequate disclosures and rationales regarding the method used for the sensitivity analysis, the variables chosen, and the ranges for those variables.⁴⁸

5. *Additional Material Information for a Balanced and Complete Presentation*

A balanced and complete presentation includes material information such as the following. FDA believes the categories of information listed below are generally material to any presentation of HCEI:

Conspicuous and Prominent Statement Describing Material Differences: If HCEI includes material differences from the FDA-approved labeling (e.g., new or increased risks, different dosing/use regimens, different endpoints, more-limited/targeted patient populations), 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

⁴⁴ See footnote 32.

⁴⁵ 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.

⁴⁶ 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.

⁴⁷ 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.

⁴⁸ See footnote 31.

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approved for the drug”⁴⁹ must be presented. For example, if a particular HCEI presentation is based on real-world data where actual patient use of the drug falls outside of the recommended dosing/use regimen in the FDA-approved labeling, the firm could include a statement such as, “The dosing regimen used in this study varies from the dosing regimen in the FDA-approved labeling,” in conjunction with the HCEI presentation and in a font size comparable to that used for the other information in the presentation. This example is not intended to suggest this is the only way for this information to be presented. In evaluating whether a statement is conspicuous and prominent, FDA considers factors such as 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.

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 of 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 balanced and complete if data or information about a product necessary to understand and contextualize the 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 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 certain studies or data sources were omitted from the analysis, the HCEI should clearly explain the reasons they were not included and how the omission 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).

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.

⁴⁹ See section 502(a).

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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 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)⁵⁰ 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 promotion⁵¹ and, therefore, is subject to FDA's requirements for submission of promotional materials. These include, but are not limited to, the postmarketing 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,⁵² the requirements regarding pre-dissemination submission of promotional materials. All supporting information for HCEI should be referenced and be made available upon request.⁵³

⁵⁰ 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*.

⁵¹ See footnote 11.

⁵² See 21 CFR 314.550, 314.640, 601.45, and 601.94.

⁵³ 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 with such information, which may include the primary data and analysis methods used to support the HCEI.

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Q.A.10. What are the Agency’s policies regarding risk-sharing and other value-based contracts between firms and payors?

A.A.10. 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, and such contracts are not subject to FDA reporting requirements.

B. Communications of HCEI by Firms to Payors Regarding Approved or Cleared Medical Devices

Q.B.1. To what extent do the recommendations described in section III.A of this guidance apply to devices?

A.B.1. Following issuance of the draft of this guidance, several commenters suggested that the recommendations describing appropriate communication of HCEI by firms to payors about approved drugs in section III.A of the guidance could also be applied to devices.⁵⁴ Although the language in section 502(a) addressing HCEI applies to drugs, not devices, FDA believes the recommendations provided in section III.A are generally applicable to device firms’ communication of HCEI to payors as well. Although section III.A refers to “drugs,” “approved indications/approved uses,” and “FDA-approved labeling,” the recommendations for “drugs” generally apply to “devices” and “approved/cleared indications/uses” and “FDA-required labeling”⁵⁵ as well. Although the HCEI language in section 502(a) is specific to drugs, the requirement in section 502(a) that information not be false or misleading applies to both drugs and devices, and the recommendations provided in section III.A can help ensure that device firms’ communication of HCEI to payors is not false or misleading. We note, however, that device firms are not subject to the same postmarketing reporting requirements to submit promotional materials as described in Q.A.9, so the information provided in A.A.9 regarding submission of promotional materials does not apply to devices.

⁵⁴ In the notice of availability of the draft version of this guidance that published in the *Federal Register* of January 19, 2017 (82 FR 6568), we specifically requested comments from interested parties on this issue (82 FR at 6568 at 6571).

⁵⁵ The term “FDA-required labeling” includes the labeling approved during the premarket approval process for a device, or, for products not subject to premarket approval but instead subject to De Novo marketing authorization, premarket notification (510(k)) requirements, or exempt from premarket review, the labeling that provides adequate directions for use and other information required to appear on the label or in labeling.

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As stated in Q.A.3/A.A.3, if a device firm disseminates HCEI that complies with the recommendations in section III.A, FDA does not intend to consider such information false or misleading or evidence of a new intended use.

C. Communications by Firms to Payors Regarding Unapproved Products and Unapproved Uses of Approved/Cleared Products⁵⁶

Medical product firms may wish to provide certain types of information to payors (as that term, used to collectively refer to payors, formulary committees, and similar entities, is described in Q.A.2/A.A.2) regarding their unapproved products and regarding unapproved uses of their approved/cleared/licensed products. Such information may help payors plan and budget for future coverage and/or reimbursement decisions prior to FDA approval, clearance, or licensure of unapproved products and may also inform coverage and/or reimbursement decisions for new uses of approved/cleared/licensed products. This section provides answers to frequently asked questions on this topic.

Q.C.1. What are the types of information covered in this section of the guidance, and what is FDA's approach with respect to firms that wish to provide such information prior to FDA approval, clearance, or licensure of an unapproved product or to provide such information about an unapproved use of an approved/cleared/licensed product?

A.C.1. When the following types of information about unapproved products (as defined in this guidance) or unapproved uses of approved/cleared/licensed products provided by firms to payors are unbiased, factual, accurate, and non-misleading, and are presented with information discussed in Q.C.2/A.C.2, FDA does not intend to object under 21 CFR 312.7(a) or 21 CFR 812.7(a) to such communications, nor to use such communications as evidence of a new intended use.⁵⁷ FDA also does not intend to enforce any applicable postmarketing submission requirements for these materials.⁵⁸

- Product information (e.g., drug class, device description and features).

⁵⁶ The draft version of this guidance contained recommendations for communications by firms to payors regarding drugs and devices that are not yet approved or cleared for any use (referred to in the draft guidance as investigational drugs and devices). FDA received many comments requesting that the Agency also provide recommendations for communications by firms to payors regarding unapproved uses of approved/cleared products. After consideration of these comments, FDA has included recommendations for such communications in this guidance.

⁵⁷ With respect to unsolicited requests by payors to firms, this guidance is not intended to supersede FDA's draft guidance for industry *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*. When final, this guidance will represent FDA's current thinking on this topic.

⁵⁸ For example, see 21 CFR 314.81(b)(3)(i), 314.550, 314.640, 601.45, or 601.94.

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- Information about the indication(s) 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).
- Anticipated timeline for possible FDA approval/clearance/licensure of the product or of the new use.
- Product pricing information.
- Patient utilization projections (e.g., epidemiological data projection on incidence and prevalence).
- Product-related programs or services (e.g., patient support programs).
- Factual presentations of results from studies, including clinical studies of drugs or devices or bench tests that describe device performance (i.e., no characterizations or conclusions should be made regarding the safety or effectiveness of the unapproved product or the unapproved use). Below are examples of appropriate, factual presentations contrasted with presentations that inappropriately characterize or make conclusions regarding safety/effectiveness. The examples illustrate just a few of the many ways firms can appropriately present results from studies. Firms should also refer to Q.C.2/A.C.2 for recommendations with respect to information they should provide when communicating to payors about unapproved products or about unapproved uses of approved/cleared/licensed products:
 - A firm intends to submit a marketing application for its product for the management of severe pain. An appropriate communication by the firm to payors may include language such as “In a X-week randomized controlled trial comparing PRODUCT to placebo, a statistically significant improvement was observed on the primary endpoint of reduction in mean pain scores from baseline” in conjunction with a graph and/or table summarizing the numerical study results.
 - By contrast, it would not be appropriate for the firm’s communication to contain language making characterizations or conclusions, such as “PRODUCT allows health care providers to optimize pain relief” or “PRODUCT has been demonstrated to provide potent pain relief.”
 - A firm recently completed a phase 3 trial evaluating its product, Drug X, for the treatment of metastatic non-small cell lung cancer, and intends to submit a marketing application for this use. An appropriate communication by the firm to payors may include language such as “In a randomized, multi-center trial of Drug X versus [active control] in patients with metastatic non-small cell lung cancer, Drug X met its

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primary endpoint of improving progression-free survival compared to [active control].”

- By contrast, it would not be appropriate for the firm’s communication to contain language making characterizations or conclusions, such as “Drug X shows superior efficacy to [active control]” or “We expect Drug X to be the drug of choice for non-small cell lung cancer.”

Q.C.2. What other information should firms provide to payors when communicating information about their unapproved products or about unapproved uses of approved/cleared/licensed products?

A.C.2. FDA recommends that firms provide the following information to payors when communicating information about unapproved products or about unapproved uses of approved/cleared/licensed products:

- A clear statement that the product or use is not approved/cleared/licensed, and that the safety or effectiveness of the product or use has not been established;
- Information related to the stage of product development (e.g., the status of any study(ies) in which a product/new use is being investigated and how it relates to the overall product development plan, whether a marketing application for the product or new use has been submitted to FDA or when such a submission is planned); and
- For communications that include factual presentations of results from studies, FDA recommends that firms describe material aspects of study design and methodology and also disclose material limitations related to the study design, methodology, and results. Firms should also ensure that results are not selectively presented (e.g., both positive and negative or null findings should be presented).

In addition, for communications to payors about unapproved uses of approved/cleared/licensed products, firms should provide:

- A prominent statement disclosing the indication(s) for which FDA has approved, cleared, or licensed the product and a copy of the most current FDA-required labeling.

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

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Q.C.3. What types of information would be considered inappropriate to communicate to payors about unapproved products or about unapproved uses of approved/cleared/licensed products?

A.C.3. Communications between firms and payors that represent that an unapproved product is FDA-approved/cleared/licensed, or has otherwise been determined safe or effective for the purpose(s) for which it is being studied would not be appropriate. Similarly, communications between firms and payors that represent that an unapproved use of an approved/cleared/licensed product is FDA-approved/cleared/licensed or that the product is safe or effective for the use(s) for which it is being studied would not be appropriate.

Q.C.4. What additional considerations apply to communications to payors about unapproved products and about unapproved uses of approved/cleared/licensed products?

A.C.4. Firms' communications regarding unapproved products and unapproved uses of approved/cleared/licensed medical products raise a number of potentially competing public health interests. FDA's approach to implementation of its authorities in this area seeks to balance these interests to best advance the public health overall.

Some firm communications regarding unapproved products or unapproved uses of approved/cleared/licensed medical products may potentially undermine substantial government interests related to health and safety. These interests include motivating the development of robust scientific data on safety and efficacy; maintaining the premarket review process for safety and efficacy of each intended use in order to prevent harm, to protect against fraud, misrepresentation, and bias, and to develop appropriate instructions for use for medical products; protecting the integrity and reliability of promotional information regarding medical product uses; and preventing the diversion of health care resources toward ineffective treatments.

FDA recognizes that there can be, in certain instances, tension between the public health interests directly advanced by the premarket review requirements and other important interests. For example, as discussed in section II of this guidance, FDA recognizes that payors, in some situations, need to plan for and make coverage and reimbursement decisions for medical products and uses far in advance of the effective date of such decisions. As a result, FDA recognizes the value of payors receiving unbiased, factual, accurate, and non-misleading information of the type described in Q.C.1/A.C.1 about unapproved products and unapproved uses of approved/cleared/licensed medical products in order to inform their decision-making.

FDA believes that the categories of information described in Q.C.1/A.C.1 are, on the one hand, broad enough to encompass the information that payors may need to

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make informed coverage and reimbursement decisions and, on the other hand, limited enough to maintain appropriate incentives for firms to conduct robust studies to evaluate the safety and efficacy of unapproved products and unapproved uses of approved/cleared/licensed medical products. In addition, if firms follow the recommendations in Q.C.1/A.C.1 and provide unbiased, factual, accurate, and non-misleading information, FDA believes that the risk that payors will be misled is relatively low. Payors are a sophisticated audience with established procedures to carefully consider the full range of relevant evidence about new uses of medical products. Payors possess financial resources and motivation to closely scrutinize information from firms. In making decisions on a population basis, payors can draw on a range of expertise in multiple disciplines that allows them to critically evaluate information presented to them by firms, including an evaluation of the limitations and reliability of that information.

Thus, FDA believes the recommendations provided in this section of the guidance appropriately balance the competing interests described above for firms' communications with payor audiences about unapproved products and unapproved uses of approved/cleared/licensed products. Firms' communications to other audiences about unapproved products or unapproved uses of approved/cleared/licensed products could raise additional or different considerations and are beyond the scope of this guidance.⁵⁹

IV. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). Specifically, the guidance contains recommendations for information that should be included when HCEI about approved prescription drugs and about approved or cleared devices is disseminated to payors. FDA also recommends that certain information be included in firms' communications with payors about unapproved products and about unapproved uses of approved/cleared products.

FDA estimates that it will take firms approximately 20 hours to compile and draft the information that this guidance recommends should be included when disseminating HCEI for

⁵⁹ The Agency has issued other guidance documents that could apply to firms' communications to other audiences. For example, FDA has issued a draft guidance for industry describing its thinking on how firms can respond to unsolicited requests for unapproved use information related to their FDA-approved prescription drugs and FDA-approved or cleared medical devices. See FDA's draft guidance for industry *Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices*. 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. See FDA's guidance for industry *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*, and FDA's revised draft guidance *Distributing Scientific and Medical Publications on Unapproved New Uses – Recommended Practices*.

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approved prescription drugs and approved/cleared devices. FDA estimates it will take firms approximately 30 minutes to compile and draft the information that this guidance recommends should be provided with communications to payors about unapproved products or unapproved uses of approved/cleared products, and that it will take about 2 hours for firms to compile and provide communications of follow-up information regarding previously communicated information to payors about their unapproved products or unapproved uses of approved/cleared products. Send comments regarding this burden estimate or suggestions for reducing this burden to:

FDA PRA Staff
Office of Operations
Food and Drug Administration
Three White Flint North
11601 Landsdown Street, 10A-12M
North Bethesda, MD 20852

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in 21 CFR 314.81(b)(3)(i) (Form FDA 2253) have been approved under OMB control number 0910-0001.

An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is 0910-0857 (expires 08/31/2024 (Note: OMB control number and expiration date added 09/28/2021)).