BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

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BY ELECTRONIC DELIVERY

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Re: AHRQ Draft Guide for Conducting Comparative Effectiveness Reviews: Public Comments from the Biotechnology Industry Organization (BIO)

The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Agency for Healthcare Research and Quality's (AHRQ) Guide to Conducting Comparative Effectiveness Reviews. BIO is the largest trade organization to serve and represent the biotechnology industry in the United States and around the globe. BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers, and related organizations. BIO members are involved in the research and development of health care, agricultural, industrial and environmental biotechnology products.

As the representative of an industry committed to discovering new therapies and ensuring patient access to them, BIO is a strong proponent of evidence-based medicine, and greatly appreciates the leadership that AHRQ has provided with its Effective Health Care initiative. Since passage of Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), BIO has advocated for an open and transparent process for conducting comparative effectiveness reviews (CERs). As such, BIO appreciates that AHRQ is seeking public comments on its draft guide, and encourages continued outreach and involvement of all interested stakeholders through the various stages of the CER process.

BIO has reviewed the draft guide, and recognizing that it is an evolving "work in progress," offers specific and general comments related to process, research methodology and application of CERs. Our comments focus on chapters 1 (overview), 2 (topic development), 3 (selecting evidence: controlled trials), 6 (assessing the quality and applicability of included studies), and 9 (Quantitative Synthesis).

Chapter 1: Overview

The overview chapter provides a concise summary of the approach to CERs indicating that they follow the "explicit principles of systematic reviews." As part of this discussion, the overview briefly details the differences between efficacy studies and effectiveness studies and explains that effectiveness studies "are intended to provide results that are more applicable to "average" patients." The overview then continues to explain how CERs might be applied stating, "payers and insurers may use them to make clinical and group policy decisions on benefits and coverage, and professional groups may base their clinical practice guidelines on them."

This initial discussion highlights a key and critical concern of the biotechnology industry – CERs often fail to take into account the unique clinical circumstances and characteristics of individual patients, as well as those with rare diseases. BIO strongly supports efforts to increase the availability of accurate, scientific evidence to inform clinical decision-making, which could include CERs, among various other types of medical evidence. However, BIO is concerned that CERs may be viewed by some strictly as a means to contain costs, rather than deliver health care value by improving patient-centered care. For example, BIO is concerned that the results of CERs could be inappropriately applied to patients with rare diseases (i.e., "orphan" conditions) or to patients who fall outside of "average" parameters, potentially jeopardizing the ability of providers to deliver the most appropriate care for each patient based on his or her individual response to therapy, preferences, complications, and genetic makeup.

BIO strongly supports the guide's assertion that "comparative effectiveness reviews do not contain recommendations and they do not tell readers what to do; judgment, reasoning, and considerations of the values of the relevant parties (patients, clinicians, decision makers, and society) must also play a role in decision making." Similarly, BIO appreciates the

explanation of the term "not proven" which states that "users of comparative effectiveness review must also keep in mind that 'not proven' does not mean an intervention is proven not effective; that is, if the evidence supporting a specific intervention is weak (i.e., strength of the evidence is judged to be low or insufficient), it does not mean that the intervention is ineffective." For example, it could mean that the study was not sufficiently powered to detect a statistically significant difference in outcomes. This is important for readers of the guide and CERs to understand. Additionally, BIO supports AHRQ's decision to incorporate additional topics which have unique considerations, such as the evaluation of diagnostic tests, into future iterations of this guide. BIO also supports regular review of existing CERs that occur in a timeframe reflective of the pace in which new evidence becomes available.

BIO builds on both of these valid and important statements, as well as the concerns mentioned above, when making the following recommendations.

- **Recommendation 1:** Discussion of the limitations and exceptions of a CER should be given significant prominence, perhaps comparable to the findings themselves. A full and thoughtful discussion about the limitations and exceptions not addressed in the comparison study is equally as important as a discussion of findings to clinical decision makers when evaluating patient specific treatments.

There should be enough information in the limitations and exceptions section of CERs for health care decision makers to address those patients for whom the study findings are not representative. As mentioned above, BIO is particularly concerned about this issue because many innovative biopharmaceutical therapies have unique qualities that may render an "average" finding not relevant. For example, patients with certain genetic characteristics may respond to and benefit more from a particular type of biological treatment compared to those with different genetic characteristics. As there is limited research on treatment efficacy that controls for (or has identified) genetic confounding, there is the potential for the findings to not apply generally to certain populations and therefore, potentially limit access to the best treatment option for these patients.

- **Recommendation 2:** Incorporate statements into the overview section of this guide to:

- Explain that because CERs focus on average patients, they may not sufficiently address patients with rare diseases, certain genetic characteristics, or unique clinical circumstances;
- Indicate that because CERs focus on specific conditions, they are not necessarily designed to address advancements in pharmacogenomics and personalized medicine; and
- Emphasize the use of CERs to inform clinical judgment and individual patient needs in medical decision making.

Chapter 2: Topic Development

The process for topic development should be transparent, open to the public, and standardized. Research topics should be selected on the basis of answering important, clinical questions, where scientific uncertainty is high, where broad and adequate research on the topic exists, and where a salient review of the topic would educate and inform patients and physicians. BIO supports AHRQ's process for seeking public nominations for CER topics. However, BIO believes that a panel comprised of AHRQ and other stakeholder representatives, including patients, providers, and clinical experts from the biopharmaceutical industry, should be responsible for reaching a consensus agreement and ultimately determining the annual topics to be studied. Medical services should be selected for CERs only when there is a sufficiently robust body of evidence to make a constructive analysis. Premature reviews of new treatments and their related uses that find there is insufficient clinical evidence may not be helpful to decision makers or patients, and may result in guidance that is counterproductive. For example, AHRQ should acknowledge that there may be inadequate evidence to assess the impact of off-label uses of biopharmaceuticals and newly approved products for which there will be a lack of evidence other than the available clinical trial data.

BIO also supports and appreciates AHRQs efforts to involve the public in the development of key questions for CER research. AHRQ should expand this public participation process and, in addition to seeking comment on key questions, allow for public input on the overall topics selected for study. In so doing, the following information about the topic should be made public:

- Origination of Request;
- Rationale for Selection of Treatment Comparators;

- Discussion of the Adequacy of Available Evidence
- Anticipated Technical Limitations;
- Proposed Members of Technical Expert Group (TEG); and
- Description of Process by which the TEG Reviews Evidence.

When selecting topics for research, it is important to maintain a broad focus on the totality of the health care delivery system, and not just on drugs and biologicals. BIO believes that all types of treatments and comparators should be evaluated using methods appropriate to the topic under consideration and accounting for unique aspects of a particular subject matter. This must include more than a limited focus on drugs, biologicals and medical devices, but include major medical procedures, diagnostic testing and screening, preventive services, clinical and disease management strategies, as each has the potential to affect patient health outcomes.

BIO believes that AHRQ's research should remain focused on the priority conditions and specific topics that are identified through public processes. If AHRQ elects to deviate from the conditions and topics identified through these public processes, BIO strongly urges AHRQ to provide the public with its rationale for focusing on non-priority conditions and outside topics. Providing such justification would increase the transparency and openness of the topic selection process, which is critical to enhancing the credibility of any comparative effectiveness research program.

BIO applauds AHRQ's efforts to establish processes for conducting CER studies that are open and transparent, and involve all stakeholders. To enhance the credibility and usefulness of any comparative effectiveness study, all stakeholders including those representing patients, physicians, clinical experts from the biopharmaceutical industry, and others should be afforded the opportunity to provide input into all steps along the study process within a sufficient timeframe to allow for thoughtful analysis and comment. Accordingly, BIO encourages AHRQ to proactively reach out to affected stakeholder communities to solicit comments on new research reviews, and to provide, at a minimum, a 60-day comment for each key phase of the study process. In addition, we encourage AHRQ to provide written responses to the public comments it receives from stakeholders, and to publish these public comments when issuing final reports. These measures would increase transparency and allow for a more meaningful dialogue with the broader scientific and stakeholder communities.

The recommendations we have made related to chapter 2 are summarized as follows:

- **Recommendation 3:** Establish a multidisciplinary consensus panel, including stakeholders from the biopharmaceutical industry, to select annual topics for study.

- **Recommendation 4:** Allow for public comment on topic selection and provide the public with relevant background information including: origination of request, rationale for selection of treatment comparators, anticipated limitations, and proposed members of the TEG, and a more transparent process by which the TEG is involved in: reviewing the data, considering public comments, and developing and revising draft reviews. Further, allow public input and comment on the assessment of the adequacy of available evidence.

- **Recommendation 5:** Ensure fair and rounded representation of CER studies to include the totality of the health care delivery system such as preventive services, major medical procedures, disease management programs, and health care delivery models.

- **Recommendation 6:** Increase transparency and stakeholder input by providing sufficient time for the public to comment on key aspects of the CER process (e.g., draft research reviews) by allowing for a minimum 60-day public comment period. In addition, to support a more meaningful dialogue with stakeholders, BIO encourages AHRQ to provide written responses to the public comments the agency receives on key questions and research reviews, and make stakeholder comments public when issuing final research reviews.

Chapter 3: Selecting Evidence: Controlled Trials

Comprehensive selection of evidence is an essential component of a sound comparative effectiveness analysis. BIO supports and understands the importance of efficacy and effectiveness studies, retrospective, and survey based research. BIO maintains, however, that comparative studies should not rely exclusively on these types of research, as they may not capture the unique benefits of many drug and biological therapies and accordingly, could bias comparison findings. We are concerned that comparative effectiveness research has the potential to ignore many important aspects of

treatment interventions that affect patients, or may not account for the full spectrum of disease severities. To account for this, we suggest that AHRQ consider the following when evaluating the available evidence for all treatments under study:

- Safety associated with different treatments;
- Patient reported:
    - Changes in quality of life associated with different treatments;
    - Preferences and satisfaction with different treatments;
    - Changes in functioning and/or behaviors, such as ability to return to work faster, associated with different treatments.

BIO also encourages the evaluation of systematic differences associated with each treatment modality. For example, studies could consider differences in:

- System-wide provision of care including types of providers and setting;
- Patient adherence to treatment and the effect this has on treatment outcomes and cost;
- Support systems that are needed for success of different treatment alternatives.

We believe that the first bullet above (i.e., provider type and site of service) is of particular importance as the U.S. healthcare delivery system is fragmented and the transition of care from one setting to the next or from one clinician to the next is not optimal. BIO questions how one could compare and evaluate interventions without considering the environment and behavior of users within the context of the patient experience.

Given these comments, our recommendations on chapter 3 are summarized as follows.

- **Recommendation 7:** Consider various types of outcomes data and evidence in CERs such as increased safety profiles, improved quality of life, patient reported preferences, and changes in worker productivity.

- **Recommendation 8:** Investigate systematic differences associated with each treatment modality, including factors such as variation in provider

type and site of service, patient adherence to treatment regimen, and characteristics that are needed for treatment success.

Chapter 6: Assessing the Quality and Applicability of Included Studies

BIO supports the use of a standardized and validated framework for evaluating the quality and applicability of included studies. The proposed rating system of quality (good, fair, poor) and applicability (population, intensity or quality of treatment, choice of, and dosing of, the comparator, outcomes, and timing to follow-up) should be reviewed with members of the TEG to reach consensus on the various components. If consensus is unattainable, discrepancies should be made available to the public.

This chapter provides an informative overview of evidence selection; however BIO recommends that AHRQ provide additional guidance on its proposed mechanism to rate the overall body of evidence of one intervention versus others in selected studies, specifically how AHRQ intends to identify and evaluate how much variation may exist between bodies of evidence for all treatments under comparison. BIO supports the conduct of CERs that focus on all treatment options available to patients (as opposed to one drug therapy over the other). Systematic differences in the amount and quality of the literature on different treatments are likely to exist. For example, the quality and applicability of research available on biologicals may be radically different than the quality and applicability of research available on an intervention of diet and exercise. Similarly, a rating system that may be appropriate when looking at highly prevalent disease states may not be appropriate when examining data for diseases with a much lower prevalence in the general population and where the data may not be as abundant. Such differences may result in a rating of "good" or "fair" in a common disease state (i.e. hypertension), where the same system might result in a "poor" rating for orphan conditions or condition that afflicts significantly fewer people. Basing comparisons on a body of literature with different levels of quality and applicability could result in bias comparisons.

Given these considerations, BIO recommends:

- **Recommendation 9:** Use of a consensus based process for the TEG to reach consensus on the rating system of quality and applicability with differences made available to the public when consensus is unattainable.

- **Recommendation 10:** Issue additional clarification on AHRQ's proposed mechanism to rate the overall body of evidence of one intervention versus others. That is, clarify how AHRQ intends to identify and evaluate variation that may exist among bodies of evidence for all treatments under comparison.

Chapter 9: Quantitative Synthesis

One very critical consideration to conducting CERs is the development of a shared understanding of when the available data reaches sufficient maturity to allow for comparison. The critical issue is how to determine when there is an adequate breadth and depth of data to allow for a clinically meaningful comparison between health care interventions. The discussion of data maturity merits only one paragraph in the guide on page 67, yet this is a recurring challenge facing developers of new health technologies throughout a product's life-cycle.

- **Recommendation 11**: BIO suggests that AHRQ address the issue of data maturity in greater detail in the guide.

Conclusion:

BIO thanks AHRQ for the opportunity to raise our issues and concerns. Despite these concerns, BIO is grateful for the efforts of AHRQ and others to expand the information available about treatments for devastating diseases and appreciates the efforts made to date to keep the process open and transparent. BIO believe that CER results can be quite useful for physicians and the patients they are treating to make informed choices and design the best possible treatments for these diseases, and we look forward to continuing to work with AHRQ to identify and implement improvements to the Section 1013 Effective Health Care Program. Please feel free to contact Ted Buckley at 202-962-6691 or John Siracusa at 202-312-9281 if you have any questions or if we can be of further assistance.