



September 22, 2006

***BY ELECTRONIC DELIVERY***

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Centers for Medicare and Medicaid Services  
Department of Health and Human Services  
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**Re: Guidance for the Public, Industry, and CMS Staff: National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development**

Dear Dr. Phurrough:

The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) guidance document entitled "National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development (CED)" ("Guidance Document").<sup>1</sup> 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

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<sup>1</sup> Guidance for the Public, Industry, and CMS Staff: National Coverage Determinations with Data Collection as a Condition of Coverage: Coverage with Evidence Development, July 12, 2006 (hereinafter "Guidance Document").

biotechnology companies, academic institutions, state biotechnology centers, and related organizations in the United States. BIO members are involved in the research and development of healthcare, agricultural, industrial and environmental biotechnology products.

BIO's members are strongly committed to increasing the body of evidence available regarding diseases and their treatments. Our members invest millions of dollars each year on clinical studies, both before and after Food and Drug Administration (FDA) approval of their products, to produce high-quality clinical evidence to support medical decision-making. We also support the dissemination of this evidence to further clinical knowledge and enhance and improve the clinical decision-making process.

Our commitment to developing evidence extends far beyond studies of a particular therapy. We support a rigorous evidence development process that encompasses all aspects of a disease from examining how it affects the body to studying the costs and benefits of therapies. Our research initiatives advance the understanding of disease pathology and therapeutic mechanisms of action, clinical effectiveness in naturalistic settings, health-related quality of life, and health economic impacts of therapies in addition to clinical safety and efficacy. The development and evaluation of therapies are part of this broader process and must be considered in context.

Our evidence development process, combined with Medicare's current coverage policies, allows beneficiaries timely access to new therapies and encourages innovation. The Medicare statute and manuals give local carriers the flexibility and freedom to make timely coverage decisions, ensuring Medicare beneficiaries' access to the latest drugs and biologicals for medically accepted uses. These policies also encourage innovation and continued research by giving patients a choice of new therapies and new uses of therapies and creating a relatively stable and predictable reimbursement environment, so critical for many of our smaller members who depend on private sector investment.

In 2005, BIO was one of many stakeholders who submitted comments on CMS' draft guidance on CED. Similar to many other interested parties, we were concerned that CED, as described in the draft guidance, could limit Medicare beneficiaries' access to innovative therapies, and we believed that the draft guidance left many critical questions unanswered. In response to these comments, CMS announced that it would

issue a second draft guidance document followed by a 30-day comment period.<sup>2</sup> We are pleased that CMS considered our comments before issuing this document but are disappointed that CMS issued a final document rather than a second draft. Although we appreciate CMS' willingness to accept comments on the Guidance Document, we believe that a second draft document, with opportunity for further stakeholder discussion and comment, would have allowed CMS to continue to develop CED in a more open and transparent manner. We request that CMS treat this Guidance Document as a second draft, revise the Guidance documents based on stakeholder comments, and issue a final Guidance document. We also request that CMS hold at least one Open Door Forum to respond to questions and allow for greater stakeholder discussion regarding the document.

We believe the Guidance Document makes significant progress toward addressing our concerns regarding the 2005 draft guidance. In general, we agree with the principles governing the application of CED described in the Guidance Document:

1. National Coverage Determinations (NCDs) requiring CED will occur within the NCD process, which is transparent and open to public comment.
2. CED will not be used when other forms of coverage are justified by the available evidence.
3. CED will in general expand access to technologies and treatments for Medicare beneficiaries.
4. CMS expects to use CED infrequently.
5. CED will lead to the production of evidence complementary to existing medical evidence.
6. CED will not duplicate or replace the FDA's authority in assuring the safety, efficacy, and security of drugs, biological products, and devices;
7. CED will not assume the National Institute of Health's (NIH) role in fostering, managing, or prioritizing clinical trials.
8. Any application of CED will be consistent with federal laws, regulations, and patient protections.<sup>3</sup>

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<sup>2</sup> Fact Sheet: CMS Responds to Stakeholder Feedback Regarding Coverage with Evidence Development, July 12, 2005.

<sup>3</sup> Guidance Document, § VII.

We ask CMS to clarify the following issues within the principles, however:

- Not only should the NCD process be open and transparent, but CMS should establish a process that allows for stakeholder input into topic selection and study design.
- CMS should provide further guidance as to the frequency and circumstances for applying CED, also specifying the evidentiary standards for both Coverage with Appropriateness Determination (CAD) and Coverage with Study Participation (CSP).
- CMS should clarify whether it expects to apply CED infrequently in relation to all coverage decisions or only to NCDs.
- CMS should clarify whether NIH or another federal agency or organization has final say over research priorities.

We urge the agency to continue to work with stakeholders to ensure that any application of CED adheres to CMS' principles and to resolve our remaining questions about CED. These questions include:

- How will CMS ensure that beneficiaries have access to appropriate care outside the context of CAD and CSP?
- How will CMS ensure that any application of CED is consistent with federal laws, regulations, and patient protections?
- How will CMS ensure that CED is applied with minimal burdens on patients, providers, and manufacturers?
- What role will the Agency for Healthcare Research and Quality (AHRQ) play in determining when to apply CED or in the studies covered under a NCD applying CED?

We discuss each of these questions in more detail below.

I. How will CMS ensure that beneficiaries have access to appropriate care outside the context of CAD and CSP?

- A. **CMS must protect access to care for beneficiaries who cannot or choose not to participate in clinical trials by ensuring that CSP does not interfere with the local coverage process.**

BIO remains concerned that CED may limit beneficiaries' access to appropriate, innovative therapies by preventing local contractors from covering therapies for beneficiaries who do not participate in clinical trials under CSP. As we explained in our comments on the draft guidance document, many Medicare beneficiaries are ineligible to participate in clinical trials due to age, comorbidities, or complications. Some beneficiaries, particularly those in rural areas or with limited incomes, may choose not to participate if the trial would require them to travel long distances to receive care. Many beneficiaries may be discouraged from participating in trials that would require them to change physicians. Beneficiaries must continue to have access to appropriate therapies, regardless of whether they participate in clinical trials.

We urge CMS to clarify that any application of CED will be used to expand access to care in clinical trials, but will not limit carriers' discretion to cover the same uses of the items or services outside the trials. Indeed, the Guidance Document should state explicitly that CMS encourages carriers to use this discretion to cover care in this circumstance. CMS used this approach in the NCD on anti-cancer chemotherapy for colorectal cancer,<sup>4</sup> and we urge the agency to use it in any future applications of CSP.

BIO requests that CMS issue guidance to carriers regarding the continuation of local coverage and clarifying that CED should not have the result of reducing coverage for beneficiaries. Specifically, we recommend that CMS clarify that carriers should not require data collection as a condition of local coverage. Also, where a local coverage determination (LCD) provides for broader coverage than a NCD with CED, and the NCD is not exclusionary, the component of the LCD that is broader than the NCD should not be subject to the CED requirements. Finally, CMS should not impose data collection requirements on local contractors and should state this explicitly in the guidance.

**B. CMS must protect beneficiary access to appropriate, innovative uses of approved drugs and biological products used in anti-cancer chemotherapeutic drug regimens outside the context of clinical trials.**

In the Guidance Document, CMS indicates that CSP may be used when “the available clinical research may have failed to address

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<sup>4</sup> Medicare National Coverage Decision Manual (CMS Pub. 100-3), § 110.17.

adequately the risks and benefits to Medicare beneficiaries of off-label or other unanticipated uses of a drug, biologic, service, or device.”<sup>5</sup> BIO urges CMS to clarify that this application of CSP will not be used in conflict with the statutory provisions requiring coverage of drugs and biological products used in an anti-cancer chemotherapeutic regimen for indications other than those approved by the FDA when the uses are supported by citations in certain compendia or are supported by peer-reviewed literature.<sup>6</sup> Congress intended for Medicare beneficiaries to have access to all appropriate therapies in their battles against cancer, and the statute establishes an efficient and evidence-based decision-making process for determining which uses Medicare must cover. We urge CMS to clarify that CSP will not interfere with the statute’s assurance of access to these important therapies.

**C. CMS must protect beneficiary access to care after an evidence development process has been completed.**

CMS also explains that the data gathered through CED may be used to develop future NCDs,<sup>7</sup> and the Guidance Document acknowledges that there may be a gap between coverage under an NCD with CED and the issuance of a new NCD.<sup>8</sup> BIO is concerned that Medicare coverage for an item or service covered under CED may be severely restricted upon the conclusion of the evidence development activity, however. The Guidance Document does not explain how coverage will be determined once data collection through a registry ends, but it notes that coverage will revert to the pre-NCD coverage policy after a research study ends.<sup>9</sup> In addition, CSP studies typically will not lead directly to expanded coverage; instead, coverage status reverts to pre-CSP policy with the expectation that the collected data will be used in future NCDs, which will unnecessarily delay beneficiary access to innovative therapies.

Instead of reverting to the pre-NCD coverage, potentially meaning that the item or service would not be covered, we believe that beneficiary access to care would be protected best by continuing to cover the item until CMS issues a new NCD. During the gap between a NCD with CED and a new NCD, CMS should allow coverage for the item or service

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<sup>5</sup> Guidance Document, § V.B.  
<sup>6</sup> SSA § 1861(t)(2).  
<sup>7</sup> Guidance Document, § VI.B.  
<sup>8</sup> Guidance Document, § VII.A.  
<sup>9</sup> Guidance Document, § VIII.A.

when provided to a beneficiary who meets the criteria for coverage set forth in the CED NCD, with the exception of participation in the data collection activity. For example, if a beneficiary would have qualified for the clinical trial, but the trial is no longer ongoing or accepting new patients, Medicare should allow coverage for the beneficiary to receive the same treatment that would have been covered under the clinical trial. Similarly, if a registry is no longer collecting data, but the treatment would have qualified for coverage if data had been reported to the registry, Medicare should cover the treatment. We urge the agency to clarify that, in the absence of a new NCD, Medicare will cover an item or service that was subject to CED for any beneficiary who would have met the requirements for participation in the data collection activity. Finally, we also urge CMS to provide further guidance on how and when data requirements will expire.

II. How will CMS ensure that any application of CED is consistent with federal laws, regulations, and patient protections?

In the Guidance Document, CMS states, “any application of CED will be consistent with federal laws, regulations, and patient protections,” including the Paperwork Reduction Act of 1995,<sup>10</sup> the Privacy Act of 1974,<sup>11</sup> the Health Insurance Portability and Accountability Act of 1996,<sup>12</sup> and the Health and Human Services (HHS) protection of human subjects regulation.<sup>13</sup> Although we applaud CMS for recognizing the importance of protecting the rights of patients who participate in clinical trials, we ask the agency to explain exactly how it will ensure that these protections are in fact provided throughout the research conducted under CED and any subsequent uses and disclosures of research data.

We are greatly concerned that CMS’ intent to collect, aggregate, and disclose research data collected through CED is incompatible with the goals of the federal laws the agency purports to obey. For example, the HHS protection of human subjects regulations are intended to ensure that clinical research is conducted in accordance with the principles of informed consent, including patient authorization for use and disclosure of health information, and institutional review board (IRB) review. These regulations require investigators to provide each patient with a “statement describing the

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<sup>10</sup> 35 U.S.C. § 3501.

<sup>11</sup> 5 U.S.C. § 552a.

<sup>12</sup> 45 C.F.R. Parts 160, 162, and 164.

<sup>13</sup> 45 C.F.R. Part 46.

extent, if any, to which confidentiality of records identifying the patient will be maintained.”<sup>14</sup> The federal privacy regulations also restrict researchers’ use and disclosure of identifiable health information for research purposes.<sup>15</sup> These regulations provide important protections that help to encourage patients to participate in clinical research. Generally, patients are reluctant to participate in research unless they are told how their data will be used and assured that their records will be kept confidential. By complying with these regulations and providing patients with accurate information about how their information will be used and to whom it will be disclosed, researchers can assure their patients that their consent truly is informed. Although an IRB may waive the informed consent requirements in certain circumstances, we believe that patients should be offered every protection possible.

To ensure that patients’ rights are protected in any clinical trials conducted under CSP, we ask CMS to state clearly that it will not collect raw data from these trials. In the guidance, CMS makes no references to actually collecting raw data from clinical trials. Instead, the guidance notes that the evidence from a clinical trial will be used in a NCD reconsideration if the research results are published in a peer-reviewed journal.<sup>16</sup> Indeed, to achieve the purposes of CSP – allowing access to care in a setting that provides greater assurances of safety and encouraging publication of trial results – the only data CMS needs is confirmation that the patient is indeed enrolled in a trial. In fact, based on our conversations with CMS staff last fall, this appears to be what CMS is doing with the clinical trials covered under the NCD for anticancer chemotherapy for colorectal cancer. If CMS were to require more data, it would risk undermining the IRB and informed consent process employed in each of these trials. We ask CMS to confirm that its use of data from any clinical trial covered under CSP will comply with the law by stating that the agency will not collect any data and thus will not aggregate or release the data to other groups.

In contrast to its discussion of clinical trials, the guidance specifically refers to CMS’ collecting, aggregating, and disclosing registry data. This raises significant concerns for registry sponsors about their ability to provide meaningful patient protections. Researchers’ efforts to ensure that their patients can provide truly informed consent to participate in these registries

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<sup>14</sup> 45 C.F.R. § 46.116(a)(5).

<sup>15</sup> 45 C.F.R. § 164.512(i).

<sup>16</sup> Guidance Document, § V.B.

would be completely nullified by CMS' re-identification and redisclosure of the data to any number of entities for any number of uses. Even if patients could be informed about the uses and disclosures of their data, their consent would be coerced if the only way they can get Medicare to cover their treatment is by agreeing to those disclosures. Additionally, any IRB waiver of informed consent for CMS to use data for reasons not described at the outset of the research would make the whole IRB process meaningless. Furthermore, CMS' assurances of compliance with the Privacy Act offer little protection because its definition of "routine uses" is so broad that it allows a wide array of entities to use the data for a wide range of reasons. To ensure that patients' rights actually are protected, CMS needs to set clear limits on how it uses and discloses the information, or better yet, not collect the information at all. Precisely how CMS plans to comply with these laws needs to be described in depth in the guidance.

III. How will CMS ensure that CED is applied with minimal burdens on patients, providers, and manufacturers?

BIO remains concerned that CED will impose substantial burdens on patients, providers, and manufacturers. CMS must ensure that participation in clinical research does not increase beneficiaries' cost of care. If beneficiaries are forced to incur greater costs for receiving care in Medicare-covered clinical trials or other evidence development programs, they will choose other, potentially less appropriate, treatment options. CMS also must minimize physicians' costs of CED. Physicians who participate in clinical trials often donate considerable amounts of time and resources to evaluating patients' eligibility for trials, data collection, and drug administration services that frequently are not reimbursed by trial sponsors. With Medicare's recent changes to reimbursement for drugs and their administration and its pending reimbursement cuts for all physician services, many physicians are less able to afford to participate in clinical research.

We recommend that CMS develop reimbursement codes and rates for non-routine services to make participation in research more financially feasible. We also recommend that CMS provide reimbursement for the routine costs of care, such as drug administration, in more clinical trials. In addition, we ask the agency to use its influence to encourage private payors to cover more care costs in clinical trials.

CMS states in the Guidance Document that the agency will not fund the non-clinical research costs of clinical trials and will not provide financial support for registry development and maintenance.<sup>17</sup> CMS also urges stakeholders to work together to provide additional support for data collection efforts.<sup>18</sup> As we stated earlier, our members make substantial investments in clinical research, and we are fully aware of the costs of supporting trials and registries. We urge the agency to recognize that imposing additional clinical research requirements on manufacturers may limit our ability to support continued innovation, especially for therapies for the Medicare population, and we recommend that CMS minimize these burdens whenever possible. For example, as described in the Guidance Document, an NCD requiring a registry under CAD might not specify a length of time for collecting data.<sup>19</sup> Instead of requiring manufacturers to support an open-ended registry, we recommend that each data collection activity have a clearly defined end point.

We also urge the agency to ensure that manufacturers will be able to benefit from the research they support by allowing timely and complete access to the data CMS collects on our therapies. Rather than allowing CMS to have sole ownership of the data, CMS should share ownership with manufacturers who sponsor a CED activity. We believe that any manufacturer that makes the considerable investment required to support research under CED should own the data produced by that activity. We also recommend that CMS require the same type of Data Use Agreement (DUA) for all entities seeking access to CED data. CMS should not establish more or less stringent requirements for certain types of stakeholders, but instead should impose the same requirements on any entity that wishes to use CMS data. CMS should clarify these data ownership and usage issues and ensure that manufacturers who sponsor research under CED have timely and complete access to the data the activity produces.

IV. What role will AHRQ play in determining when to apply CED or in the studies covered under an NCD applying CED?

In the Guidance Document, CMS introduces the “new concept of conducting research under section 1862(a)(1)(E) [of the Social Security

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<sup>17</sup> Guidance Document, § X.

<sup>18</sup> *Id.*

<sup>19</sup> Guidance Document, § VIII.B.

Act] to add to the existing body of medical evidence.”<sup>20</sup> Section 1862(a)(1)(E) prohibits payment for any item or service that is not reasonable and necessary to carry out the purposes of section 1142 of the Social Security Act. Section 1142 instructs AHRQ to conduct and support research regarding the outcomes, effectiveness and appropriateness of health care services and procedures;<sup>21</sup> establish priorities for the diseases, disorders, and other health conditions for which the research will be conducted;<sup>22</sup> and develop treatment-specific or condition-specific practice guidelines to improve the quality of care provided.<sup>23</sup> AHRQ also is required to assure that the needs and priorities of the Medicare program are reflected in the development of the guidelines and research priorities,<sup>24</sup> and use those guidelines to improve the quality, effectiveness, and appropriateness of care provided under the Medicare program.<sup>25</sup>

Although CMS accurately describes these sections of the statute as allowing Medicare coverage for services provided to patients enrolled in clinical research studies conducted under section 1142, it does not explain the role of AHRQ in identifying, conducting, or supporting these studies. Instead, the only indication of AHRQ’s role in Medicare coverage of clinical research studies is suggested by CMS’ references to covering trials that meet “the standards of a qualified trial as will be outlined in the revision of the Clinical Trial Policy.”<sup>26</sup> Under the current Clinical Trial Policy, AHRQ helped to define the qualifying criteria for Medicare coverage of clinical trials by deeming certain trials sponsored or supported by the federal government to be automatically qualified for Medicare coverage.<sup>27</sup> Because CMS has not yet released a proposed new Clinical Trial Policy, it is not clear whether the agency intends for the AHRQ to take on a different role in determining which trials will be covered by Medicare or in supporting those trials. If CMS intends to revise the role of the AHRQ in the application of CED before it issues the draft decision memorandum under the reconsideration of the clinical trial policy, we urge the agency to explain its plans to stakeholders and to allow opportunity for public input.

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<sup>20</sup> Guidance Document, § I.  
<sup>21</sup> SSA § 1142(a)(1)(A).  
<sup>22</sup> SSA § 1142(b)(1).  
<sup>23</sup> SSA § 1142(a)(3)(A).  
<sup>24</sup> SSA § 1142(a)(1)(B) and (b)(3).  
<sup>25</sup> SSA § 1142(a)(3)(B).  
<sup>26</sup> Guidance Document, § VI.B.  
<sup>27</sup> National Coverage Determinations Manual § 310.1.

V. Conclusion

BIO appreciates this opportunity to comment on the Guidance Document regarding the use of CED. We hope our recommendations help CMS to apply CED in a predictable manner that ensures beneficiary access to innovative drugs and biologicals and the proper medical devices and technologies used to deliver them to patients. We look forward to working with CMS to protect Medicare beneficiaries' access to innovative drugs and biologicals. If you have any questions regarding our comments, please contact me at 202-962-9200. Thank you for your attention to this very important matter.

Respectfully submitted,

/s/

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