August 9, 2006

BY ELECTRONIC DELIVERY

Steve Phurrough, M.D.
Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mailstop: C1-12-28
7500 Security Blvd.
Baltimore, MD 21244

Re: NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R)

Dear Dr. Phurrough:

The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) Tracking Sheet regarding the development of a Clinical Research Policy (CRP) as a reconsideration of its national coverage decision (NCD) on Medicare coverage of clinical trials.[1] 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 in the United States. BIO members are involved in the research and development of healthcare, agricultural,

[1] NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R) (hereinafter "Tracking Sheet").

industrial and environmental biotechnology products. Our research initiatives advance the understanding of disease pathology and therapeutic mechanisms of action, clinical effectiveness, health-related quality of life, and health economic impacts of therapies in addition to clinical safety and efficacy.

CMS is developing the CRP in conjunction with the agency's recent "Guidance for the Public, Industry, and CMS Staff on NCDs with Data Collection as a Condition of Coverage: Coverage with Evidence Development (CED)" that was issued on July 12, 2006. As BIO has stated in our past comments regarding CED, we are committed to increasing the body of evidence available regarding diseases and their treatments. Our members spend millions of dollars each year on clinical studies, both before and after Food and Drug Administration (FDA) approval of their therapies, 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 clinical decision-making.

BIO also is committed to ensuring beneficiary access to innovative biological therapies. To that end, we support CMS' efforts to clarify its NCD on Medicare coverage of clinical trials. We believe that a clarification of Medicare's coverage policy for clinical trials has the potential to strengthen the ability of biotechnology companies to develop and evaluate innovative therapies that will specifically benefit Medicare patients. BIO urges CMS to consider its proposed CRP in light of our continued concerns regarding the CED concept. Additionally, we ask that CMS look at the broader effect that these policies have on Medicare coverage of clinical trials and beneficiary access to them. We plan to comment separately on the July 12, 2006 CED guidance and ask that those comments be taken into account for purposes of the CRP's development too.

We urge CMS to clarify the NCD in a manner that promotes Medicare beneficiary enrollment into clinical trials and assures them of coverage for their routine medical costs while enrolled in these clinical trials. Specifically, BIO requests that CMS expressly include clinical trials exempt from the investigational new drug application (IND) process, as well as establish a mechanism for other research studies to qualify for Medicare coverage. In addition, although BIO strongly supports CMS' goal of encouraging greater participation of Medicare beneficiaries in clinical trials, we urge CMS to carefully develop any guidelines regarding the representation of Medicare beneficiaries in Medicare-covered trials in a manner that reflects the challenges of enrolling Medicare beneficiaries and fosters the goal of increasing the participation of such patients rather than limiting the number of trials available to this population. Third, we continue to urge CMS

to set any data collection standards in a manner that achieves CMS' specific goals without imposing undue burdens on patients, providers, and clinical trial sponsors. Finally, we ask that CMS clarify that a sponsor's agreement to make payment for *uncovered* expenses relating to illness or injury resulting from the trial does not make the sponsor a primary payer under the Medicare Secondary Payer rules.

We have set forth these preliminary comments more fully below, and we look forward to the opportunity to comment on the proposed CRP.

I. Coverage of IND-Exempt Trials and Other Research Studies

When CMS issued the NCD for clinical trials in 2000, the agency included a list of trials automatically "deemed" to be qualified as covered by Medicare. This list included trials conducted under an IND reviewed by FDA. CMS also included as "deemed," drug trials that are IND-exempt only until other qualifying criteria were developed. Criteria were not subsequently published for the IND-exempt trials, and thus IND-exempt trials have continued to operate as "deemed" under a temporary status.

BIO urges CMS to permanently extend deemed status to IND-exempt trials in the CRP. This category of clinical trials is carefully regulated. FDA permits a clinical investigation of a drug product lawfully marketed in the United States to be exempt from the IND process only if certain requirements are met.[2] This exemption is intended to apply primarily to researchers "who are beginning to explore new uses for marketed drugs (*i.e.* not pivotal studies) or who are using the drug as a research tool."[3] An IND-exempt investigation also is permitted only where safety is not an issue and the investigation is not being conducted to support a labeling change such as a new indication or a comparative safety claim.[4]

FDA expressly has encouraged use of this IND-exempt process for qualifying trials. For example, in 2004, FDA urged the oncology industry not to submit INDs for all clinical research for oncology products but instead to use the IND-exempt process where possible.[5] Clinical trials operating under the IND-

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[2] 21 C.F.R. § 312.2(b); 52 Fed. Reg. 8798, 8801 (Mar. 19, 1987) (noting that "a study of a marketed drug involving an indication contained in the product's approved labeling would be subject to all relevant [IND] requirements" but would be "exempt from IND submission requirements if it met the conditions of § 312.2").
[3] 48 Fed.Reg. 26720, 26721 (June 9, 1983); *see also* 52 Fed.Reg. 8798, 8799-8800 (Mar. 19, 1987).
[4] *Id.*
[5] Food and Drug Administration, "Guidance for Industry, IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer," January 2004, available at www.fda.gov/cder/guidance/6036fnl.htm.

exempt process have been influential in the post-approval development of many important therapies, and this is increasingly true as more companies seek to use the IND-exempt process, at FDA's urging. Permanently adding IND-exempt trials to the list of clinical trials "deemed" qualified for Medicare coverage will reduce uncertainty among patients and providers regarding Medicare coverage for routine medical costs.

BIO also is concerned about CMS' intention to remove the self-certification process that never was implemented as part of the 2000 clinical trial NCD. We understand that an inter-agency panel met and developed criteria for the types of trials that should be covered under this process. We encourage the agency to release the panel's findings to the public and to propose an alternative qualifying process for those research studies that are not deemed to be qualifying clinical trials. This is necessary to ensure that Medicare beneficiaries have access to the full range of research studies being conducted and are able to participate in the studies that are most appropriate for their conditions.

II. Regulation of IND-exempt Trials

BIO is concerned about CMS' suggestion in the Tracking Sheet that the CRP will attempt to "[c]larify the scientific and technical roles of Federal agencies in overseeing IND Exempt trials."[6] As discussed above, IND-exempt trials are regulated by FDA. FDA has established a clear set of criteria for such trials as well as issued guidances for industry to use in determining which trials are appropriate for the IND-exempt process. We believe that the jurisdiction to regulate such trials clearly lies with FDA, and we do not believe that CMS' involvement in clarifying the scientific and technical roles of Federal agencies in overseeing these trials is a proper exercise of CMS' authority. We note that CMS is a payer for health services. Using this authority, CMS may examine whether an item or service meets criteria for coverage, and CMS may establish a list of clinical trials and other research studies that qualify for Medicare coverage of routine costs. CMS is not tasked with regulating or overseeing clinical trials, and we urge CMS not to assume the responsibilities of other agencies by seeking to participate in the oversight of clinical trials. BIO urges CMS to work with FDA and the criteria established by FDA for IND-exempt trials.

III. Increased Clinical Trial Participation by Medicare Beneficiaries

[6] NCA Tracking Sheet for Clinical Trial Policy (CAG-00071R).

BIO supports CMS' goal of encouraging more Medicare beneficiaries to participate in research studies. We believe that CMS' efforts to clarify Medicare coverage of clinical trials by developing a new CRP could have the effect of making clinical trials more available to Medicare beneficiaries. In the Tracking Sheet, CMS proposes developing criteria to assure that any Medicare covered clinical research study includes a representative sample of Medicare beneficiaries by demographic and clinical characteristics. Although BIO supports the goal of increasing Medicare beneficiary access to clinical trials, BIO is concerned that setting specific criteria requiring certain levels of Medicare enrollees in a clinical trial could have the effect of limiting beneficiary access to clinical trials.

As CMS no doubt is aware, many Medicare beneficiaries are ineligible for clinical trials due to age, comorbidities, or complications. Others may choose not to participate if the trial would require them to travel, change physicians, or experience other substantial inconvenience. This may be particularly true for patients in rural areas, minorities, and women, who traditionally have been under-represented in clinical trials. BIO urges CMS to develop a policy that recognizes the many impediments to enrolling Medicare beneficiaries in clinical trials. In order to ensure that Medicare coverage is available to those beneficiaries who do qualify for and choose to enroll in clinical trials, it is critical that CMS not impose stringent criteria that in fact hinder beneficiary participation in clinical trials.

BIO also encourages CMS to take additional steps to make Medicare beneficiaries more aware of ongoing clinical trials for which they may be eligible. BIO supports increased use of the NIH clinical trials registry as one means of educating Medicare beneficiaries about available clinical trials, and BIO urges CMS to consider other methods of more broadly disseminating this information as well.

IV. CED and New Data Collection Requirements

As mentioned briefly above, BIO currently is drafting comments to the July 12, 2006 CED guidance, and these comments also will be relevant to the CRP. We ask that CMS take our CED comments into account when developing the CRP proposed decision memorandum. Overall, BIO supports a rigorous evidence development process that encompasses all aspects of a disease. We greatly appreciate the agency's recent clarifications regarding the potential application of CED, particularly which it will be used infrequently and generally will be used to expand access to technologies and treatments for Medicare

beneficiaries. Nonetheless, we continue to have some concerns regarding the potential application of CED to drugs and biological products. Most relevant to the CRP, we are concerned about the imposition of data collection requirements in addition to those required by FDA. To the extent that CMS sets forth any data collection requirements in the CRP, we urge CMS to set data collection standards that can achieve its specific goals while imposing minimal burdens for patients, providers, and clinical trial sponsors.

The data collection required by CMS, when in addition to any FDA-required data, adds to the costs of a clinical trial. We urge CMS to take every effort to minimize these costs and to pay particular attention to the costs imposed on beneficiaries and providers. Beneficiaries' cost of care should not increase as the result of increased data collection requirements. If beneficiaries are forced to incur greater costs for receiving care in Medicare-covered clinical trials they will choose other, potentially less appropriate, care options. CMS also must minimize physicians' costs in operating clinical trials. 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.

In determining whether additional data collection is necessary for Medicare covered trials, we urge CMS to carefully balance the value of the information gathered against the burden of collecting it, align any data collection requirements with FDA's clinical study requirements and with other research priorities to ensure that our research resources are used efficiently, and require that data collection continue only as long as important questions remain and the effort and resources required to collect this data are justified by the potential value of the information to be collected. We believe it is critical that data collection needs be determined at the outset so that the study will produce the data needed to satisfy CMS' needs and to ensure that any coverage decisions relying in part on such data will be made in an efficient and timely manner. We also urge CMS to consider ways to compensate physicians more appropriately for the data collection activities they undertake, as well as services they provide relating to evaluating patient eligibility and drug administration.

In the Tracking Sheet, CMS notes that the CRP will attempt to "[c]larify how items /services that do not meet the requirements of 1862(a)(1)(A) but are of potential benefit can be covered in clinical research studies as an

outcome of the National Coverage Determination process."[7] We believe this inquiry more appropriately belongs in the CED policy, and we look forward to commenting on this issue as part of our comments on the CED guidance.

V. Medicare Secondary Payer (MSP) Issues

In developing the CRP, BIO urges CMS to clarify that when a clinical trial sponsor, study site, or investigator assures a study subject that he or she will not be responsible for out-of-pocket payments for medical services resulting from a trial-related illness or injury, that assurance will not turn the sponsor, site, or investigator into a primary payer, and render Medicare a secondary payer.

The Medicare statute requires payment for items and services that are reasonable and necessary for the treatment of illness or injury.[8] It is clear that medically necessary services provided to treat complications arising in the course of a clinical trial are intended to be covered by Medicare. Indeed, CMS regulations specifically authorize Medicare payment for complications arising from clinical trials involving the use of medical devices.[9] In addition, the current NCD itself calls for coverage by defining routine costs in qualifying clinical trials to include items and services for the treatment of complications.[10]

The Medicare Secondary Payer (MSP) statute provides that Medicare payment "may not be made…with respect to any item or service to the extent that payment has been made or can reasonably be expected to be made" under a "primary plan."[11] The statute defines "primary plan" to include (1) a group health plan or large group health plan and (2) a worker's compensation law or plan or automobile or liability insurance policy or plan (including a self-insured plan) or no fault insurance.[12] Nothing in the MSP statute or its legislative history suggests that Congress intended to expand the reach of the MSP provisions to preclude Medicare payment for covered items and services when the sponsor of a clinical

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7 *Id.*

8 42 U.S.C. §§ 1395(d) (entitlement to have payment made for inpatient hospital services), 1395k(a)(1) (entitlement to have payment made for medical and other health services), 1395y(a)(1)(A) (exclusion for items that are not reasonable and necessary for treatment of illness or injury).

9 42 C.F.R. § 405.207(b). The regulation calls for payment even when the device itself is unapproved, making clear that coverage also is compelled where the device is an approved one.

10 Medicare Coverage, Clinical Trials, Final National Coverage Decision, *available at* http://www.cms.hhs.gov/coverage/8d2.asp.

11 42 U.S.C. § 1395y(b)(2)(A).

12 *Id.* In the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), Congress amended the definition of "primary plan" to state that "[a]n entity that engages in a business, trade, or profession shall be deemed to have a self-insured plan if it carries its own risk (whether by a failure to obtain insurance, or otherwise) in whole or in part." Social Security Act § 1862(b)(2)(A).

trial offers in an informed consent document and related clinical trial agreement to make payment for *uncovered* expenses relating to illness or injury resulting from the trial. In effect, such an interpretation of the MSP statute would turn clinical trial sponsors into primary health care insurers -- a result surely not intended by Congress, and one that runs contrary to the policy of encouraging the participation of Medicare beneficiaries in clinical trials. Accordingly, BIO urges that the CRP explicitly clarify that a promise by a clinical trial sponsor or study site to pay for uncovered trial-related illness or injury will not result in the sponsor being viewed as a "primary plan," or render the sponsor, site, or investigator a "primary payer," under the MSP provisions. CMS should assure beneficiaries that they will not be denied coverage merely because they have volunteered to participate in a clinical trial.

In addition, we ask that CMS clarify that neither the MSP statute, nor the exclusion from Medicare coverage for items or services for which a person has no legal obligation to pay[13] operate to eliminate Medicare coverage for otherwise covered items where the sponsor has agreed to cover those clinical care costs that would not, in any event, have been recognized as an expense covered by insurance (e.g., the costs of care for uninsured trial participants). CMS should make clear that beneficiaries may not be denied coverage for otherwise covered items or services as a result of having volunteered to participate in a clinical trial whose sponsor has agreed to cover those clinical care costs that are not, for any particular patient, normally (i.e., absent the trial) covered by insurance.

VI. Conclusion

BIO appreciates this opportunity to comment on CMS' efforts to developed a proposed CRP, and we look forward to commenting on the proposed CRP once it is issued. We hope that our recommendations are useful to CMS in developing a proposed CRP that establishes Medicare coverage of clinical trials in a predictable manner that ensures beneficiary access to innovative drugs and biologicals. Specifically, we urge CMS to:

- Expressly designate clinical trials exempt from the IND process as "deemed" as well as establish a mechanism for other research studies to qualify for Medicare coverage;
- Carefully develop any guidelines regarding the representation of Medicare beneficiaries in Medicare-covered trials in a manner that reflects the

13/ 42 U.S.C. § 1395y(a)(2).

challenges of enrolling Medicare beneficiaries and fosters the goal of increasing the participation of such patients rather than limiting the number of trials available to this population;

- Set any data collection standards in a manner that achieve CMS' specific goals without imposing undue burdens on patients, providers, and clinical trial sponsors; and
- Clarify that Medicare coverage of a clinical trial is not conditioned on the clinical trial sponsor serving as a primary payer for certain medical costs that may be associated with the trial.

We look forward to working with CMS to encourage increased Medicare beneficiary access to and participation in clinical trials. As this is an important policy for BIO and its members, we would be pleased to have the opportunity to discuss our comments with you in greater detail. If you have any questions regarding our comments, please contact me at 202-312-9273. Thank you for your attention to this very important matter.

Sincerely,

/s/

Jayson Slotnik
Director, Medicare Reimbursement &
Economic Policy

cc: Leslye K. Fitterman
Tamara Syrek Jensen