BIO
BIOTECHNOLOGY
INDUSTRY ORGANIZATION

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***BY ELECTRONIC DELIVERY***

Steve Phurrough, MD, MPA
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: Proposed Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)**

Dear Dr. Phurrough:

The Biotechnology Industry Organization (BIO) appreciates this opportunity to comment on the Centers for Medicare and Medicaid Services' (CMS) Proposed Coverage Decision Memorandum for the Use of ESAs in Cancer and Related Neoplastic Conditions (hereinafter "Proposed NCD"). 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. In particular, many of our members are involved in the research and development of cancer therapies and play a critical role in delivering treatments that both prolong life and reduce the burden of disease for cancer patients worldwide.

In the Proposed NCD, CMS proposes a series of broad coverage restrictions on both the Food and Drug Administration (FDA) approved uses and off-label uses of ESAs in cancer-related anemia. BIO has a strong interest in this matter because CMS' proposal could establish a precedent that affects Medicare patient access to a wide range of innovative drug and biological therapies on a national basis. Such a policy approach, if more broadly adopted by CMS, could have far-reaching implications for other patient populations and treatments of other serious and life-threatening diseases.

Given the extensive comments submitted by practicing oncologists and other relevant stakeholders, BIO is concerned that the Proposed NCD could curtail legitimate, medically appropriate uses of FDA-approved ESA therapy that are supported by the scientific evidence and widely accepted clinical practice guidelines. Specifically,

clinical experts in the oncology community have questioned the completeness and rigor of CMS' review of the scientific evidence upon which the agency's coverage proposals are based. As a general principle, BIO strongly urges CMS to strictly follow sound principles of evidence-based medicine in formulating coverage policies and ensure that any coverage limitations on ESAs are firmly grounded in the available clinical evidence. BIO is also concerned that, based upon CMS' review of the evidence, the agency appears to be substituting is own conclusions regarding the safety and effectiveness of approved uses of ESAs for those of FDA. BIO urges CMS to acknowledge the important role of the FDA and its experts in evaluating the safety and effectiveness of approved indications of drugs and biologicals. Therefore, CMS should delay finalizing the Proposed NCD until after the FDA has completed its current clinical review of the safety and effectiveness of ESA therapy. Finally, BIO requests that CMS ensure that its coverage policies do not interfere with the ability of practitioners to make patient-centered treatment decisions, especially in oncology, and that CMS abide by the statutory protections for anti-cancer therapy.

## I. Medicare Coverage Decisions on Drugs and Biologicals Should Be Firmly Supported by the Scientific Evidence.

BIO recognizes CMS' statutory authority to provide Medicare coverage only for those health care items and services that the agency determines are reasonable and necessary for the diagnosis or treatment of illness or injury.[1] However, it is imperative that CMS rely on a strong evidentiary foundation when making national coverage determinations that affect Medicare beneficiary access to care, particularly when such determinations result in coverage restrictions. BIO is a strong supporter of evidence-based medicine, and believes that clinical decisions made by physicians and patients should be based on the best available scientific evidence. Evidenced-based medicine "de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision-making and stresses the examination of evidence from clinical research."[2] The Proposed NCD seems to conflict with the evidence-based coverage standards that CMS has endeavored to uphold by not evaluating the totality of the scientific evidence, and reaching conclusions that contradict the medical judgment of experienced clinical oncologists. Indeed, Dr. S. Gail Eckhardt, Chair of FDA's Oncology Drugs Advisory Committee (ODAC) recently commented, "I was shocked to see how the CMS restrictions go way beyond the scientific evidence that indicates what's actually proven beneficial or not beneficial…"[3] CMS appears to be proposing coverage restrictions on ESAs based on an unproven theoretical premise regarding the safety of the products in certain instances, and placing the burden on the manufacturers to prove this premise wrong. BIO is concerned by the potential precedent of this approach to Medicare coverage because it lacks firm

[1] Social Security Act § 1862(a)(1)(A).
[2] Dr. Steve Phurrough, "Medicare Coverage Decisions: Balancing Competing Demands." National Health Policy Conference Presentation, February 2, 2005, available at: http://www.academyhealth.org/nhpc/2005/phurrough.pdf.
[3] *The Cancer Letter*, May 18, 2007, Vol. 33 No. 19

grounding in the available scientific evidence. BIO urges CMS to strictly adhere to the principles of evidence-based medicine when making coverage decisions that affect Medicare beneficiary access to ESAs, as well as other drug and biological therapies.

BIO is concerned that the specific coverage restrictions on ESAs in the Proposed NCD lack clear support in the scientific evidence, and contradict the established standard of care. Several of the proposed restrictions are inconsistent with widely accepted clinical practice guidelines, and have been questioned by members of the practicing oncology community who have submitted comments to the Proposed NCD. For example, many clinical experts in oncology disagree that the scientific evidence supports CMS' proposed non-coverage for the use of ESAs in chemotherapy regimens that include certain drug and biological therapies. Clinical experts also disagree that the evidence supports restrictions on the coverage of ESAs to only patients with hemoglobin levels of <9 g/dl immediately prior to initiation of dosing for the month. In light of these concerns, BIO strongly urges CMS to ensure that the final NCD is well-supported by the full body of scientific evidence, and that any coverage restrictions do not inappropriately limit medically accepted uses and further restrict the FDA labeled indications.

## II. CMS Should Acknowledge the Role of the FDA in Evaluating the Safety and Effectiveness of Approved Uses of Drugs and Biologicals.

As a payer of health care services, CMS has the authority to provide Medicare reimbursement for health care items and services that the agency determines are reasonable and necessary. FDA's mission is to promote and protect the public health, which includes the approval of drugs and biologicals based upon demonstration of safety and effectiveness for the conditions of use prescribed in the labeling.[4] FDA has approved two ESAs for oncology indications and continues to monitor and assess the safety and effectiveness of these products. FDA worked with the manufacturers to change the full prescribing information for the products earlier this year, and the ODAC recently recommended that: FDA consider additional labeling changes; that additional safety studies be conducted; and that the committee reconvene to consider additional issues and recommendations to FDA.

In light of the pending FDA review and action, implementation of the coverage restrictions outlined in this Proposed NCD is premature. Disregarding the FDA's safety and effectiveness review of ESAs would essentially result in CMS creating a second set of prescribing guidelines in addition to FDA, and would result in the inability of Medicare patients to access the approved treatment to the full extent of the labeling. The four corners of the approved labeling—as agreed upon by experts in oncology and other related areas of medicine, both within and outside of FDA, and as implemented to meet a particular patient's needs—would become less relevant in light of these Medicare coverage realities. Thus, CMS should delay finalizing this NCD until

[4] FDA Modernization Act of 1997 (P.L. 105-115); Section 505(d) of the Federal Food, Drug and Cosmetic Act.

FDA has considered the results of the May 10, 2007 ODAC and completed its reevaluation of the ESA labels. In addition, CMS should take into account the results of the FDA's review prior to implementing any Medicare coverage restrictions.

Also of significant concern to BIO is the statement in the Proposed NCD that CMS is interested in public comments addressing whether access to ESAs should be limited to patients who are enrolled in clinical research trials with informed consent and safety monitoring. BIO strongly disagrees with any efforts to limit coverage of all uses of an approved drug or biological solely to patients enrolled in clinical research trials. Such an unprecedented action would be inconsistent with the status of ESAs as approved by FDA to provide safe and effective treatment for anemia in cancer patients, and with recent actions and recommendations by FDA and ODAC. It would also significantly interfere with the ability of physicians to provide proper care and treatment to their cancer patients. Limiting coverage of ESAs only to those in clinical trials would discriminate against Medicare beneficiaries who are unable to enroll in such trials due to factors beyond their control (e.g., proximity to an approved study site). Not all community oncologists are clinical investigators, and this restriction would place an undue burden on providers who would be required to administer the research protocol. Additionally, making coverage available only to beneficiaries enrolled in clinical trials could be considered coercion. Medicare patients should not be pressured into signing informed consent forms and participating in clinical trials in order to access ESAs or any other FDA-approved therapies. Given the aforementioned concerns, BIO urges CMS not to implement such unprecedented restrictions in cancer care.

## III. CMS Should Not Interfere with Physician Judgment in Medical Decision-Making, Especially in Oncology.

BIO is also deeply concerned that CMS' proposal would interfere with the ability of clinicians to make appropriate treatment decisions based on the unique clinical circumstances of each patient, and could effectively limit beneficiary access to medically appropriate therapies. Patients respond differently to the same treatment interventions based on a variety of clinical factors. This is especially true in the case of innovative drug and biological therapies, which often target specific mechanisms of action that allow particular therapies to work in specific patient populations. In order to achieve the best possible health outcomes, practitioners must have the flexibility to tailor the appropriate course of treatment for each patient based on individual clinical circumstances. In addition, many new uses of drugs and biologicals are found to be effective in very small, unique patient populations for whom FDA-approved labeling is difficult to obtain. Imposing coverage requirements that fail to adequately allow for practitioner flexibility and variations among patients can interfere with the ability of providers to deliver the most appropriate care, and could lead to suboptimal health outcomes.

The ability of clinicians to make patient-centered treatment decisions based on the scientific evidence is particularly important in oncology. In oncology, the standard of care advances approximately every six months, if not sooner, as clinical

research discovers effective new treatment regimens. Many of these treatment options involve drugs and biologicals for indications not initially approved by the FDA. Congress recognized the critical role of protecting Medicare beneficiary access to medically appropriate uses of drug and biological therapies in fighting cancer when it enacted the Medicare statute's requirement to cover off-label indications of drugs used in anticancer regimens when listed in the recognized compendia.[5] Medicare contractors are also granted the discretion to ensure beneficiary access to important drugs and biologicals if they determine that the use is supported by peer-reviewed medical literature or that the use is "medically accepted generally as safe and effective for the particular use."[6]

The Proposed NCD would eliminate Medicare coverage for certain unapproved uses of ESAs in oncology, including anemia of myelodysplasia (MDS) and anemia of myeloid cancers. This would severely limit the treatment options available to cancer patients and their doctors, and undermine the Congressional protections for anti-cancer therapy to the extent that such uses are medically accepted in the recognized compendia and established in the medical literature. By eliminating coverage for many off-label uses of ESAs, many cancer patients who would benefit from such treatment could be effectively denied it. Further, many cancer patients currently rely on ESAs to tolerate the side effects of other chemotherapy agents. By restricting coverage for ESAs, CMS could, by default, also limit access for other effective anti-cancer therapies used as part of a chemotherapy regimen. In finalizing the NCD, CMS should consider these consequences, and recognize the critical role of the physician in determining and delivering the most appropriate care for each Medicare patient.

## IV. CMS Should Remain Consistent with Current Statutory Protections for Anti-Cancer Therapy and Adhere to the FDA Label.

Due to the existing statutory protections for Medicare beneficiary access to anti-cancer therapies, CMS should adhere to the approved indications of ESAs until further action by the FDA. Doing so is not only necessary to ensure that Medicare patients maintain access to medically appropriate cancer treatments, but also is consistent with the laws that govern Medicare coverage policies. In 1993, Congress enacted legislation that was intended to resolve questions about the discretion of Medicare officials and contractors to limit coverage of medically appropriate cancer therapies. Accordingly, in §1861(t)(2) of the Social Security Act (42 U.S.C. §1395x(t)(2), the term "drugs" is specifically defined to include "any drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication," which is further defined to include "any use which has been approved by the Food and Drug Administration" as well as any compendia-supported use that has not been found by the Secretary to be medically inappropriate.

[5] Social Security Act § 1861(t)(2)(B)(i)(I).
[6] Social Security Act § 1861(t)(2)(B)(i)(II); Medicare Benefit Policy Manual (CMS Pub. 100-2), ch. 15, § 50.4.5.

In enacting this legislation, Congress clearly intended for Medicare beneficiaries to have access to on-label and off-label uses of medically appropriate cancer therapies. BIO believes that CMS is acting contrary to this Congressional intent and is doing so without an evidentiary basis with regard to the coverage limitations applicable to on-label uses of ESAs. In addition, the statute provides that if off-label coverage is to be restricted in a manner that conflicts with compendia references, there must be a specific determination by the Secretary that the restricted uses are medically inappropriate. There is no evidence supporting such a determination.

## V. Conclusion

In conclusion, BIO sincerely hopes that CMS will give thoughtful consideration to our comments and concerns prior to finalizing this NCD. If you have any questions regarding our comments, please contact John Siracusa at 202-312-9281. Thank you for your attention to this very important matter.

Respectfully submitted,

/s/

Sandra J.P. Dennis
Deputy General Counsel for Health Care Regulatory Affairs

/s/

John A. Siracusa
Manager, Medicare Reimbursement and Economic Policy

cc: Louis Jacques, MD
Maria Ciccanti, RN
Tara Turner, PharmD
Elizabeth Koller, MD, FACE
Shamiram Feinglass, MD, MPH