WASHINGTON LEGAL FOUNDATION
2009 Massachusetts Avenue, N.W.
Washington, DC 20036
202-588-0302

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Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Services
Department of Health and Human Services
Mail Stop: C1-09-06
7500 Security Blvd.
Baltimore, Maryland 21244

Re: Proposed Decision Memorandum for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (CAG-00383N)

Dear Dr. Phurrough:

The Washington Legal Foundation (WLF) appreciates the opportunity to submit comments to the Centers for Medicare and Medicaid Services (CMS) on the above-referenced proposed decision memorandum for Erythropoiesis Stimulating Agents (ESAs) for Non-Renal Disease Indications (hereafter NCD). WLF is a non-profit public interest law and policy center based in Washington, D.C., with supporters nationwide. WLF promotes free market policies through litigation, administrative proceedings, publications and advocacy before state and federal government agencies, including CMS and the Food and Drug Administration (FDA).

As set forth below, WLF urges CMS to withdraw its proposed national coverage determination for ESAs for the following reasons:

(1) CMS does not have authority under the Social Security Act to limit or eliminate coverage for FDA-approved uses of ESAs in cancer treatment regimens. The statute requires CMS to provide coverage for such products when used for "medically accepted indications." A medically accepted indication includes any use approved by FDA.

(2) The CMS determination would constitute arbitrary and capricious decision-making in violation of the Administrative Procedure Act. That is because the Secretary of Health and Human Services (HHS) is ultimately responsible for decisions by CMS and FDA, and here each agency has reached different and irreconcilable conclusions on the same set of facts about the benefit-risk profile of ESAs.

(3) Beyond being unlawful, CMS's intrusion into FDA's area of expertise will adversely affect the delivery of patient care and development of new medications. The proposal could lead to malpractice allegations against physicians who use an ESA contrary to Medicare coverage criteria. The CMS decision also unsettles legal doctrines critical to a manufacturer's decisions regarding drug development.

I. Background: The CMS's Proposed National Coverage Determination for ESAs

In its decision memorandum for ESAs, CMS proposes no longer to cover ESA treatment for the following conditions:

- Any anemia in cancer or cancer treatment patients due to foliate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis.
- The anemia of myelodysplasia.
- The anemia of myeloid cancers.
- The anemia associated with the treatment of myeloid cancers or erythroid cancers.
- The anemia of cancer not related to cancer treatment.
- Any anemia associated with radiotherapy.
- Prophylactic use to prevent chemotherapy-induced anemia.
- Prophylactic use to reduce tumor hypoxia.
- Patients with erythropoietin-type resistance due to neutralizing antibodies.
- Patients with treatment regimens including anti-angiogenic drugs such as bevacizumab (Avastin).
- Patients with treatment regimens including monoclonal/polyclonal antibodies directed against the epidermal growth factor receptor (EGFR).
- Anemia due to cancer treatment if patients have uncontrolled hypertension.
- Patients with thrombotic episodes related to malignancy.

Moreover, while CMS indicated that it would continue to cover the use of ESAs for certain types of cancer, it proposes to do so only under the following additional conditions relating to dosing and duration of therapy:

- The hemoglobin/hematocrit levels immediately prior to initiation of dosing for the month should be less than 9 g/dl/27% in patients without known cardiovascular disease and less than 10 g/dl/30% in patients with documented symptomatic ischemic disease that cannot be treated with blood transfusion. The latter patients should be alerted to the increased potential for thrombosis and sequelae.

- The maximum covered treatment duration is 12 weeks per year.

- The maximum covered four-week treatment dose is 126,000 units for erythropoietin and 630 µg for darbepoietin.

In support of these proposed determinations, CMS cites "emerging safety concerns" about ESAs, and it declares that it is responding to FDA's decision to add black box warnings to the labels of all ESAs. CMS has, however, gone well beyond FDA's determination for ESAs by, in effect, concluding that the benefit-risk balance of ESAs requires their use in narrower circumstances than those approved by FDA. Indeed, while FDA would allow for continued marketing of ESAs under more stringent conditions, CMS would withhold coverage in certain situations because of what it perceives to be the deleterious effects of ESAs. As a result, the CMS proposal, if finalized, would override FDA's determination of the benefit-risk balance for these products and have the effect of denying patients access to approved uses of ESAs.

II. Interests of the Washington Legal Foundation

The Washington Legal Foundation is a public interest law and policy center with supporters in all 50 States. Since its founding in 1977, WLF has engaged in litigation and advocacy to defend and promote individual rights and a limited and accountable government, including in the area of patients' rights. For example, WLF successfully challenged the constitutionality of FDA restrictions on the ability of doctors and patients to receive truthful information about off-label uses of FDA-approved medicines. *Washington Legal Found. v. Friedman*, 13 F. Sup. 2d 51 (D.D.C. 1998), *appeal dism'd*, 202 F.3d 331 (D.C. Cir. 2000). A panel of the federal appeals court in Washington recently ruled in WLF's favor in its challenge to FDA restrictions on patient access to developmental drugs. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470 (D.C. Cir.), *reh. en banc granted*, 2006 U.S. App. LEXIS 28974 (D.C. Cir. 2006). WLF is currently engaged in litigation with CMS regarding CMS's restrictions on patient access to information about Medicare Part D prescription drug benefits. *Fox v. Leavitt*, No. 06-1490 (D.D.C.). WLF has previously submitted comments to CMS on February 10, 2004, and June 25, 2004, concerning Medicare coverage of off-label uses of FDA-approved cancer drugs under Part B, Part D, and the Section 641 demonstration program. WLF also submitted comments to CMS on June 6, 2005, concerning the agency's draft

guidance entitled, "Factors CMS considers in Making a Determination of Coverage with Evidence Development."

III. The CMS Is Not Authorized Under the Social Security Act to Deny or Limit Coverage for FDA-Approved Uses of ESAs in Cancer Treatment Regimes

At the outset, WLF must emphasize that CMS does not have authority under the Social Security Act to limit or eliminate coverage for FDA-approved uses of ESAs by asserting that such therapy is not safe and, therefore, not necessary or reasonable. Under Section 1832 of the statute, a beneficiary of the Medicare program is entitled to payment made to him, or on his behalf, for "medical and other health services." 42 U.S.C. § 1395k(a)(1). For the purposes of the statute, "medical and other health services" are defined to include, among other things, "services and supplies (including drugs and biologicals which are not usually self-administered by the patient) furnished as an incident to a physician's professional service . . . ." 42 U.S.C. § 1395x(s)(2)(A). The terms "drugs" and "biologicals" are defined to include those products that are "included . . . in the U.S. Pharmacopoeia, the National Formulary, or . . . in New Drugs or Accepted Dental Remedies." 42 U.S.C. § 1395x(t)(1).

While the foregoing statutory provisions provide coverage for various types of pharmaceuticals, the Medicare statute also includes provisions that specifically mandate coverage of drugs and biologicals used in oncology settings. Section 1861(t)(2)(A) of the Social Security Act directs CMS to provide coverage for "drugs or biologicals used in an anticancer chemotherapeutic regimen for a medically accepted indication." 42 U.S.C. § 1395x(t)(2)(A). The CMS has previously indicated that, for the purposes of this provision, a cancer treatment regimen includes a drug (such as an ESA) that is used to treat toxicities or side effects of the cancer treatment regimen when the drug is administered incident to a chemotherapy treatment.[1] A "medically accepted indication" includes any use which has been approved by FDA for the drug. 42 U.S.C. § 1395x(t)(2)(B).

In the instant case, CMS would deny coverage for approved uses of drugs and biologics utilized in anticancer chemotherapeutic regimens upon a finding that such coverage is not reasonable and necessary because it is not safe. To be sure, Section 1862(a)(1) of the Social Security Act authorizes CMS to deny coverage for items and services that are not determined to be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." 42 U.S.C. § 1395y(1)(A). The statutory terms "reasonable" and "necessary" have, however, been consistently construed by CMS to mean that a product must be safe and effective, medically necessary, and not experimental. And, for the purposes of determining safety and efficacy, CMS has routinely relied on the findings of FDA that a drug or biologic is safe and effective for its approved uses.

[1] See Centers for Medicare & Medicaid Services, Medicare Benefit Policy Manual, CMS Pub. 100-02, § 50.4.5, *Unlabeled Use for Anti-Cancer Drugs* (Oct. 1, 2003).

The CMS may not now invoke the reasonable and necessary requirement in the Medicare statute to second-guess FDA's determinations about the safety and efficacy of approved ESAs. Indeed, while Congress expressly authorized the Secretary of HHS to limit coverage for medically inappropriate off-label uses of anticancer products, it chose not to establish the same exception for uses approved by FDA. Specifically, under Section 1861(t)(2)(B)(ii)(I) of the Act, the Secretary must generally provide coverage for an off-label use of an anticancer product if such use is supported by inclusion in certain authoritative compendia. That coverage, however, may be withheld where the Secretary has determined that the use is not "medically appropriate." 42 U.S.C. § 1395x(t)(2)(B). In contrast, by not authorizing the Secretary to make similar determinations for approved uses, Congress made clear that CMS may not base coverage decisions for approved anticancer products on its assessment of whether a particular use is "medically appropriate."[2]

IV. The CMS Coverage Determination Would Constitute Arbitrary and Capricious Action Under the Administrative Procedure Act

Even assuming arguendo that CMS's coverage determination for ESAs is somehow permissible under the Social Security Act, it would nonetheless constitute arbitrary and capricious decision-making on the part of the Secretary of Health and Human Services, in violation of the Administrative Procedure Act. 5 U.S.C. § 706(2)(A). The Secretary is, of course, ultimately responsible for determining what claims are covered for drugs and biologics under the Social Security Act. 42 U.S.C. § 1395x(t)(2)(A). Pursuant to the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. § 355(d), and Public Health Service Act (PHSA), 42 U.S.C. § 262, the Secretary is also responsible for authorizing approval and marketing of drugs and biological products.[3] In connection with issuance of the proposed coverage determination, and on the basis of the same facts, the Secretary has reached different and irreconcilable positions about the benefit-risk profile of ESAs under these separate federal statutes. That is arbitrary and capricious decision-making.

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[2] *See e.g., Russello v. United States*, 464 U.S. 16, 23 (1983) ("Where Congress includes particular language in one section of a statute but omits it in another section of the same Act, it is generally presumed that Congress acts intentionally and purposely in the disparate inclusion or exclusion."); *City of Chicago v. Environmental Defense Fund*, 511 U.S. 328, 338 (1994) ("[I]t is generally presumed that Congress acts intentionally and purposely when it includes particular language in one section of a statute but omits it in another."); *S. D. Warren Co. v. Me. Bd. of Envtl. Prot.*, 126 S. Ct. 1843, 1852 (2006) ("[W]hen Congress fine-tunes its statutory definitions, it tends to do so with a purpose in mind."); *Sosa v. Alvarez-Machain*, 542 U.S. 692, 712 n.9 (2004) (observing that one party's request that the Court read a phrase into a statute, "when it is clear that Congress knew how to specify [that phrase] when it wanted to, runs afoul of the usual rule that when the legislature uses certain language in one part of the statute and different language in another, the court assumes different meanings were intended.") (internal quotation omitted).

[3] *See* Federal Food, Drug, and Cosmetic Act of 1938 §505(d), 21 U.S.C. § 355(d) (establishing a finding of safety and effectiveness as a precondition to approval of a new drug application); *see also* § 351 of the Public Health Service Act, 42 U.S.C. § 262 (providing that biologics license applications are to be approved "on the basis of a demonstration that the biologics product...is safe, pure, and potent...").

Although the Secretary has delegated his responsibilities under the SSA and the FDCA/PHSA to CMS and FDA, respectively, he is nonetheless the federal official charged by Congress with responsibility for administering these statutes. As described at the outset, the Secretary (acting through FDA) chose to address the safety concerns raised about ESAs by requiring black box warnings, updated warnings, and a change to the dosage and administration sections for all ESAs. With these changes, however, the Secretary decided to allow continued marketing of ESAs for use in all oncology settings.[4] On the other hand, the Secretary (acting through CMS) has reached a different conclusion about the benefit-risk balance of ESAs than FDA (the expert agency on such matters), and he proposes to withdraw coverage for approved uses of ESAs in certain anticancer chemotherapeutic regimens. This inconsistency in decision-making by the Secretary is improper under the APA.

Under the APA, a federal agency's actions, findings, and conclusions may not be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law. 5 U.S.C. § 706(2)(A). In determining whether an agency acted in a manner consistent with this provision, the courts look to whether the decision-maker has "considered the relevant factors and articulated a 'rational connection between the facts found and the choice made.'" *Motor Vehicle Mfrs. Ass'n of the U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Applying that standard here, the Secretary cannot satisfy this test since, on the same set of facts, he has reached conflicting conclusions about the safety profile of ESAs. While CMS may assert that the Secretary's actions can be harmonized because its coverage decisions are different than FDA's determinations, that argument misses the point. Here, the Secretary has acted in an arbitrary and capricious manner because he has reached different conclusions about the underlying benefit-risk profile of ESAs.

V. The CMS Determination Would Seriously Undermine the Existing Regulatory Framework Governing Patient Care and the Development of New Medicines

By basing its proposed NCD on an analysis of the safety profile of ESAs, CMS has intruded into FDA's area of expertise and authority in a manner that will have serious adverse implications for the delivery of patient care and the development of new medications. CMS's prior determinations on Medicare coverage of drugs and devices have generally related to circumstances that FDA had not addressed. Typically, Medicare coverage determinations concern off-label uses of drugs[5] or the utility in specific clinical situations of diagnostic devices

[4] FDA may further revise the labeling for ESA products in light of the meeting of the Oncologic Drugs Advisory Committee (ODAC) on May 10, 2007. At this point, however, the risk profile upon which CMS based its decision and the determination itself are inconsistent with FDA's evaluation of the risk-benefit profile and decision to allow continued marketing.

[5] *See, e.g.*, Centers for Medicare & Medicaid Services, CMS Pub. 100-03, Medicare National Coverage Determinations Manual § 200.1, *Nesiritide for Treatment of Heart Failure Patients* (Mar. 2, 2006) (denying coverage for Nesiritide when used off-label to treat congestive heart failure); *id.* § 110.17, *Anticancer Chemotherapy for Colorectal Cancer* (Jan. 28, 2005) (providing for coverage of the off-label use of oxaliplatin, irinotecan, cetuximab, and bevacizumab in specific clinical trials).

that have broad applications.[6] The CMS proposal on ESAs is the first time, to our knowledge, that CMS has second-guessed FDA's determination of a product's benefit-risk balance with respect to conditions of use that FDA has approved.

That intrusion into FDA's area of expertise would deny patients access to medicines that FDA has determined to be safe and effective. This denial would not be based on any issue within the expertise of CMS as administrator of a healthcare insurance program, but rather on CMS overriding FDA's determination of the benefit-risk balance. If CMS has authority to ignore FDA's conclusions, patient access to many approved therapies could be threatened. Moreover, while the ESA proposal involves restrictions on the use of drugs, if CMS can make its own determinations about benefit-risk balance, it also could expand Medicare coverage to uses considered *unsafe* by FDA. For example, CMS might conclude, contrary to FDA's determination, that a less expensive drug could safely be used in a particular situation instead of a more expensive alternative. If FDA's safety determination was correct, the result of CMS's policy would be harmful to patients.

In addition, CMS's coverage determination may decrease patient access to ESAs by opening the door to malpractice allegations against physicians who use a drug in accordance with its FDA-approved labeling but contrary to Medicare coverage criteria, even in the case of non-Medicare patients. Since CMS's proposal would effectively declare to be unsafe certain conditions of use that FDA has approved as safe, a patient injured by an FDA-approved use of the product could cite the Medicare coverage policy to support a malpractice action if that patient were prescribed the medication in a manner that was inconsistent with the NCD. Although the nuances of medical malpractice law vary from state to state, the basic malpractice analysis considers whether a practitioner has acted in a manner that a similarly situated "reasonable" practitioner would not have.[7] It is possible that a jury would give weight to CMS's conclusions about the benefit-risk balance of a product in assessing whether a practitioner acted reasonably, which could give rise to increased malpractice liability risk for those practitioners who prescribed medications for uses outside of the NCD. This heightened risk might discourage practitioners from prescribing the medication in a manner inconsistent with the NCD, which

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[6] *See, e.g., id.* § 220.6, *Positron Emission Tomography (PET) Scans* (Apr. 4, 2005) (listing all Medicare-covered uses of positron emission tomography scans); *id.* § 220.5, *Ultrasonic Diagnostic Procedures* (Oct. 2, 2003) (setting forth procedures for which Medicare coverage is extended and identifying procedures that are considered experimental and should therefore not be covered).

[7] *See, e.g., Locke v. Pachtman*, 521 N.W.2d 786, 789 (Mich. 1994) ("Proof of a medical malpractice claim requires the demonstration of the following four factors: (1) the applicable standard of care, (2) breach of that standard of care by the defendant, (3) injury, and (4) proximate causation between the alleged breach and the injury.") (citing Mich. Comp. Laws § 600.2912a); *Rogers v. Meridian Park Hosp.*, 772 P.2d 929, 932 (Ore. 1989) ("Medical malpractice cases are nothing more than negligence actions against medical professionals. The fundamental issue in these cases, as in all negligence cases, is whether the defendant breached the standard of care and caused injury to the plaintiff."); *Hood v. Phillips*, 554 S.W.2d 160, 165 (Tex. 1977) ("The burden of proof is on the patient-plaintiff to establish that the physician-defendant has undertaken a mode or form of treatment which a reasonable and prudent member of the medical profession would not have undertaken under the same or similar circumstances."); *Duckworth v. Bennett*, 181 A. 558, 559 (Pa. 1935) ("A physician is required to exercise only such reasonable skill and diligence as is ordinarily exercised in his profession.").

could have the untoward effect of denying patients medication to which they otherwise would have had access.

CMS's proposal would also unsettle legal doctrines that are relevant to the risk-reward calculation that figures into pharmaceutical manufacturers' decision-making regarding drug discovery and development. Centralizing the review of drug safety and efficacy within one regulatory agency (i.e., FDA) enhances the efficiency of the drug development process, allowing manufacturers to gain experience with the agency and the regulatory framework in which it operates. FDA takes the position that it conducts a comprehensive evaluation of a product's benefits and risks under the conditions of use in the proposed labeling, and that States are therefore not permitted to upset FDA's judgment by imposing further requirements such as additional warnings.[8] FDA's position precludes courts from holding pharmaceutical manufacturers liable for injuries based on a theory that State law required the manufacturer to provide warnings that FDA did not require.

Although FDA's position has been accepted by some courts, it has been rejected by others[9] and the issue has not been finally resolved. *Compare Ehlis v. Shire Richwood, Inc.*, 233 F. Supp. 2d 1189, 1198 (D.N.D. 2002) *with Motus v. Pfizer*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000). CMS's assertion of authority in the ESA case threatens to further undermine FDA's position and helps support an argument against FDA preemption of State law. For example, if a federal agency like CMS can recalculate FDA's benefit-risk balance for Medicare coverage purposes, it is difficult to see why a State should be prohibited from recalculating it for product liability purposes. CMS's action thus jeopardizes FDA's position on preemption and injects a level of regulatory unpredictability into the drug development process. WLF is concerned that CMS's position will discourage funding for research and development. In considering whether to expend the enormous sums required to obtain FDA approval of a new drug, companies will be reluctant to do so if the FDA-approved conditions for use can be ignored by Medicare or if FDA determinations regarding safety and efficacy could be disregarded by other federal or State agencies.

Finally, it is important to note that explicit regulation of drug labeling by States may become permissible if CMS's action is sustained. For example, the California Supreme Court invalidated an effort under that State's Proposition 65 to require a warning on nonprescription nicotine replacement therapy products. *Dowhal v. SmithKline Beecham Consumer Healthcare*, 32 Cal. 4th 910 (2004). In reaching that decision, the court deferred to FDA's judgment that the State warning on nicotine risks, although truthful, was preempted by FDA's expert determination that the State warning would create a greater risk by discouraging use of the products. *Id.* at 930-34. If CMS can override FDA's expert determinations on comparative benefits and risks, courts

[8] *See* 71 Fed. Reg. 3922, 3933-3936 (Jan. 24, 2006).

[9] *See, e.g., Motus v. Pfizer, Inc.*, 127 F. Supp. 2d 1085 (C.D. Cal. 2000), *summary judgment granted*, 196 F. Supp. 2d 984, 986 (C.D. Cal. 2001), *aff'd*, 358 F.3d 659 (9th Cir. 2004).

may see little basis for preventing States from regulating products based on a risk assessment different from FDA's.

Accordingly, for the foregoing reasons, WLF urges CMS to withdraw its proposed NCD for ESAs. The proposal is clearly unlawful under the Social Security Act and the Administrative Procedure Act. It also would seriously undermine the regulatory framework governing the delivery of patient care and development of new medications. Thank you for your consideration of these comments.

Sincerely,

/s/ Daniel J. Popeo
Daniel J. Popeo
Chairman and General Counsel

/s/ Richard A. Samp
Richard A. Samp
Chief Counsel