Filgrastim-sndz (ZARXIO)

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Filgrastim-sndz is the first biosimilar drug approved in the USA; the reference product is filgrastim (NEUPOGEN). It is a white blood cell growth factor that regulates the production of neutrophils in the bone marrow and affects neutrophil proliferation, differentiation, and some end-cell functions.
Indication(s) Under Review in this document (may include off label)	Filgrastim-sndz is a leukocyte growth factor indicated to: • Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associate with a significant incidence of sever neutropenia and fever. • Reduce the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of patients with acute myeloid leukemia (AML). • Reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g. febrile neutropenia, in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by bone marrow transplantation. • Mobilize autologous hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. • Reduce the incidence and duration of sequelae of severe neutropenia (e.g. fever infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.
Dosage Form(s) Under Review	Single-use pre-filled syringe, 300 mcg/0.5ml and 480 mcg/0.8ml
Basis for and Extent of Biosimilarity and Interchangeability with Reference Product	☒ **Biosimilar** to US reference product or to non-US reference product bridged to US reference product; intervention by the prescribing health care provider is required when substituting the biologic product for the reference product. ☐ **Interchangeable**; the biologic product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. ☐ Data from actual clinical use supports interchangeability ☒ Same approved indications ☐ Lacks indication(s) for ____ (for which the reference product has approval)

REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy Rating	Pregnancy Category C. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Executive Summary	
Efficacy	• Filgrastim-sndz is biosimilar, by FDA standards, to the reference filgrastim product licensed in the U.S. and to the licensed product in the EU. • The clinical trial submitted for USA approval was a phase III trial in breast cancer patients receiving standard neo-adjuvant therapy. • Filgrastim-sndz and filgrastim produced similar reductions in duration of severe neutropenia and met non-inferiority bounds. • There were no antibody formations found with either product. • Absolute Neutrophil Count (ANC) time course was superimposable. • Alternating the biosimilar and reference product on different cycles did not seem to affect outcome.
Safety	• Adverse events in breast cancer trial were similar between products and expected based on reference product adverse reactions: Treatment emergent adverse events 20.6% biosimilar vs 19.6% reference • Package insert lists common adverse reactions from reference labeling. • Low incidence of serious adverse reactions.
Other Considerations	• Do not administer to patients with latex allergy.
Projected Place in Therapy	• Filgrastim-sndz has been shown to be biosimilar to the reference filgrastim product licensed in the U.S. • Due to episodic use, switching between products should not be problematic. • One product could serve as a workhorse agent with the other 2 available for patient-specific reasons (e.g. allergy) or for potential shortages of workhorse.

Background

Purpose for review

Issues to be determined

- ✔ Evidence of need
- ✔ Does filgrastim-sndz offer advantages to currently available alternative?
- ✔ Does filgrastim-sndz offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives	Other Considerations	CFU, Restrictions or Other Guidance
Filgrastim (Neupgen)	Reference product. Long term experience. Available as both pre-filled syringe and vial.	Only for Hepatitic C related neutropenia
Tbo-filgrastim (Granix)	Only 1 indication. Only pre-filled syringes	
Sargramostim (Leukine)	GM-CSF; not interchangeable	
Non-formulary Alternative (if applicable)	**Other Considerations**	
Pegfilgrastim (Neulasta)	Pegylated formulation; only requires 1 dose. Not for all indications.	

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to April 2016) using the search terms EP2006 and filgrastim sandoz. The search was limited to the Pub Med Clinical Queries Filter for Therapy (specific/narrow and sensitive/broad) and studies performed in humans and published in the English language. Reference lists of review articles and evidence based databases were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Biosimilarity in USA

- Definition: "that the biological product is highly similar to the reference product not withstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product."
- Must demonstrate product is biosimilar to a single reference product previously licensed by the FDA. The sponsor may seek to use data derived from animal or clinical studies comparing the product to a non-U.S.-licensed comparator product if able to provide adequate scientific justification and bridge to the U.S.-licensed product.
- FDA using a Totality-of-the –Evidence approach to include structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and comparative clinical data.

Filgrastim-sndz

- Product quality attributes: Tier 1: Potency and Protein concentration (content). Equivalence with the reference product using state of the art testing (e.g. cell proliferation assay and reversed phase chromatography) and a two one sided t-test. Filgrastim-sndz meets equivalence to both the US and the comparator product from the EU.
- Other tier attributes: amino acid sequence, target binding, higher-order structure (i.e. correct folding), microheterogeneity of product variants, process-related impurities, and stability profile. The biosimilar, the reference product, and the comparator (bridge) all found to be biosimilar. [1]
- PK/PD[2]
  - Protein characterization: Expressed using recombinant E. coli strain. Sequencing patterns of the primary structure of the biosimilar, USA comparator and EU comparator were comparable in all samples and confirmed with identical data using mass spectrometric analyses. A high degree of congruence in secondary and tertiary structures was also seen.
  - All products were of similar high purity.
  - No differences between products with regard to low-level variants due toprocess-related impurities.
  - Biological characterization: Low variability and no differences in kinetic rate constants.
  - PD/PK data: N=28 healthy nonsmoking or ex-smoker adults age 18-49. Mean Absolute Neutrophil Count (ANC)-time profiles were comparable. Bioavailability after administration of biosimilar slightly lower than comparator but the 90%CI for AUC and C_{max} were within standard boundaries confirming bioequivalence.
  - Safety: Incidence of treatment-emergent AEs similar between groups. Most were mild. No relevant differences in severity, type or pattern of AEs between groups.

Table #1 Clinical trial for US approval

Study	Setting	Pts	ECOG PS	Treatment	Response (%)	PFS months	OS months
EP2006 to reference in breast cancer[3] <u>Study design</u> Randomized, double-blind, multicenter phase III trial	Breast cancer patients scheduled to receive neo-adjuvant chemotherapy with docetaxel, doxorubicin, and cyclophosphamide. Adequate bone marrow function. Exclusion: history of myelogenous leukemia, myelodysplastic syndrome or concomitant sickle-cell disease, concurrent or prior radiotherapy within 4 weeks, use of prophylactic antibiotics, prior chemotherapy, or anticancer treatment of breast cancer or previous G-CSF.	Pooled biosimilar =107 Pooled reference =107	≤2	4 treatment groups: Biosimilar (B) Reference (R) Alternate between B and R 5 mcg/kg/day subcutaneously from day 2 of each cycle until ANC recovered to $10X10^9$/l after its nadir or for a maximum or 14 days	**Duration of Severe Neutropenia (DSN) during Cycle 1** **Mean DSN:** **B- 1.17±1.11 days** **R-1.20±1.02 days** **Mean treatment difference 0.04 days with lower limit of 97.5%CI of -0.26 days (predefined noninferiority margin -1 day)** Mean ANC time course was superimposable Fever in 13.5% of alternating and 9.3% of nonalternating arm over all cycles FN leading to hospitalization: 1.1% alternating arm vs 2.3% nonalternating arm. Safety: no patient developed binding or neutralizing antibodies against G-CSF.		

- This trial demonstrates biosimilarity with no clinically meaningful differences between biosimilar and reference product. Alternating products did not seem to adversely affect outcomes.
- Animal, PK/PD studies, and single-arm clinical trials from the EU comparator product were also used as part of the submission.
- Extrapolation of efficacy and safety data from one indication to another may be used if biosimilarity between products has been established. [4]
- Development of the EU biosimilar Zarzio followed a similar pathway to determine biosimilarity.[5]
- Experience with the biosimilar EU comparator product in Europe, via the approval process and in small postmarketing studies provides an additional level of support.[6,7]

Potential Off-Label Use

This section is not intended to promote any off-label uses. Off-label use should be evidence-based.

- Anemia in myelodysplastic syndrome.
- Peripheral Blood Progenitor Cell Collection from donors in allogeneic bone marrow transplant.

Safety [8]

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• Patients with a history of severe allergic reactions to human granulocyte colony-stimulating factors such as filgrastim, or pegfilgrastim products.
Warnings/Precautions	• Fatal splenic ruptures- evaluate patients with left upper abdominal or shoulder pain for an enlarged spleen or splenic rupture. • Acute respiratory distress syndrome (ARDS)-evaluate patients who develop fever and lung infiltrates. • Serious allergic reactions, including anaphylaxis-permanently discontinue in patients with serious allergic reactions. • Fatal sickle cell crisis • Capillary Leak Syndrome-Episodes vary in frequency and severity and may be life-threatening. Monitor for hypotension, hypoalbuminemia, edema, and hemoconcentration. • Severe chronic neutropenia- The risks and benefits of continuing therapy of patient develops abnormal cyotogenetics or myelodysplasia should be considered. Transformation to myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) have been reported in the natural history of SNC without cytokine therapy and SCN during therapy with filgrastim products. • Thrombocytopenia • Leukocytosis-Discontinue filgrastim therapy if ANC surpasses 10,000/mm^3 after chemotherapy-induced ANC nadir. Monitor CBS's twice weekly during therapy. When used for peripheral blood progenitor stem cell collection, discontinue when leukocyte count is > 100,000/mm^3. • Cutaneous vasculitis – hold therapy in cases of cutaneous vasculitis. Therapy may be restarted when symptoms resolve and ANC decreases. • Potential effect on malignant cells - Some tumors contain the G-CSF receptor. The possibility exists that filgrastim products act as a growth factor for these tumors. The safety of filgrastim in CML and MDS has not been established. • Simultaneous use with chemotherapy or radiation therapy – Safety and efficacy of simultaneous use with chemotherapy has not been established. Do not administer within 24 hours before through 24 hours after cytotoxic chemotherapy. Avoid simultaneous use with radiation therapy as safety and efficacy have not been established.

Safety Considerations

- Significant cardinal adverse reactions: musculoskeletal pain and injection site reactions.
- Do not administer to patients with latex allergy.

Adverse Reactions

Common adverse reactions	• Nonmyeloid malignancies receiving chemotherapy: pyrexia, pain, rash, cough and dyspnea. • AML: pain, epistaxis and rash. • Nonmyeloid malignancies undergoing chemotherapy followed by BMT: rash • Peripheral blood cell mobilization: bone pain, pyrexia and headache.

	• Symptomatic with severe chronic neutropenia: pain, anemia, epistaxis, diarrhea, hypoesthesia and alopecia.
Death/Serious adverse reactions	5% vs 2% (reference product)
Discontinuations due to adverse reactions	None

Drug Interactions

Drug-Drug Interactions
None

Risk Evaluation

As of 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	Filgrastim-sndz: filgrastim, tbo-filgrastim, pegfilgrastim Zarxio: Zaroxolyn, Zarontin • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations

- Patients with latex allergies should not administer filgrastim-sndz (Zarxio) prefilled syringes, because the needle cap contains natural rubber latex (derived from latex).
- Subcutaneous injection: administer in the outer area of upper arms, abdomen, thighs, or upper outer areas of buttock.
- Dilution: If required for IV administration, filgrastim-sndz may be diluted in 5% Dextrose Injection, USP to concentrations between 5 mcg/mL and 15 mcg/mL. Dilutions in this range should be protected from adsorption to plastic materials with the addition of Albumin (Human) to a final concentration of 2 mg/mL. When diluted in 5% Dextrose Injection, USP, or 5% Dextrose Injection, USP plus Albumin (Human), filgrastim-sndz is compatible with glass, polyvinylchoride, polyolefin, and polypropylene.
- DO NOT DILUTE WITH SALINE at any time, as product may precipitate.
- Zarxio should be stored in the refrigerator at 2ºc to 8ºC (36 to 46ºF) in the original pack to protect from light. Do not shake. Do not freeze. May be allowed to come to Room Temperature before administration for a maximum of 24 hours.
- The FDA Oncology Drug Advisory Committee (ODAC) noted that the amino acid structure of EP2006 was identical to the reference product, but that the buffer used in formulation was different which could lead to differences in chemical properties but any differences would be minor with regard to clinical activity.

Dosing and Administration

- Myelosuppressive chemotherapy or induction and/or consolidation chemotherapy for AML: Recommended starting dosage of filgrastim-sndz is 5 mcg/kg/day, administered as a single daily injection by subcutaneous injection, by short intravenous infusion (15 to 30 minutes), or by continuous intravenous infusion. Obtain a complete blood count (CBC) and platelet count before instituting filgrastim-sndz therapy and monitor twice weekly during therapy. Consider dose escalation in increments of 5 mcg/kg for each chemotherapy cycle, according to the duration and severity of the absolute neutrophil count (ANC) nadir. Recommend stopping filgrastim-sndz if the ANC increases beyond 10,000/mm^3.
- Dosage in patients undergoing bone marrow transplantation: The recommended dosage of filgrastim-sndz following bone marrow transplantation (BMT) is 10 mcg/kg/day given as an intravenous infusion no longer that 24 hours. Administer the first dose of filgrastim-sndz at least 24 hours after cytotoxic chemotherapy and at least 24 hours after bone marrow infusion. Monitor CBCs and platelet counts frequently following marrow

transplantation. During the period of neutrophil recovery, titrate the daily dosage of filgrastim-sndz against the neutrophil response.

Table #2 Recommended Dosage Adjustments during Neutrophil Recovery in Patients with Cancer following BMT

Absolute Neutrophil Count	Filgrastim-sndz Adjustment
When ANC greater than 1000/mm^3 for 3 consecutive days	Reduce to 5 mcg/kg/day[a]
Then, if ANC remains greater than 1000/mm^3 for more than 3 consecutive days	Discontinue filgrastim-sndz
Then, if ANC decreased to less than 1000/mm^3	Resume at 5 mcg/kg/day

[a] If ANC decreases to less than 1000/mm^3 at any time during the 5 mcg/kg/day administration, increase filgrastim-sndz to 10 mcg/kg/day, and then follow the steps above.

- Dosage in patients undergoing autologous peripheral blood progenitor cell collection and therapy: The recommended dosage of filgrastim-sndz for mobilization of autologous peripheral blood progenitor cells (PBPC) is 10 mcg/kg/day given by subcutaneous injection. Administer filgrastim-sndz for at least 4 days before the first leukapheresis procedure and continue until the last leukapheresis. Although the optimal duration of filgrastim-sndz administration and leukapheresis schedule have not been established, administration of filgrastim for 6 to 7 days with leukapheresis on days 5, 6, and 7 was found to be safe and effective. Monitor neutrophil counts after 4 days of filgrastim-sndz, and discontinue filgrastim-sndz if the white blood cell (WBC) count rises to greater than 100,000/mm^3.
- Dosage in patients with severe chronic neutropenia: Prior to starting filgrastim-sndz in patients with severe chronic neutropenia, confirm the diagnosis of severe chronic neutropenia (SCN) by evaluating serial CBCs with differential and platelet counts, and evaluating bone marrow morphology and karyotype. The use of filgrastim-sndz prior to confirmation of a correct diagnosis of SCN may impair diagnostic efforts and may thus impair or delay evaluation and treatment of underlying condition, other than SCN, causing the neutropenia. The recommended staring dosage in patients with Congenital Neutropenia is 6 mcg/kg as a twice daily subcutaneous injection and the recommend staring dosage in patients with Idiopathic or Cyclic Neutropenia is 5 mcg/kg as a single daily subcutaneous injection.
    - Dosage adjustments in SCN: Chronic daily administration is required to maintain clinical benefit. Individualize dosage based on the patient's clinical course as well as ANC. In the SCN post-marketing surveillance study, the reported median daily doses of filgrastim were: 6 mcg/kg (congenital neutropenia), 2.1 mcg/kg (cyclic neutropenia), and 1.2 mcg/kg (idiopathic neutropenia). In rare instances, patients with congenital neutropenia have required doses great than or equal to 100 mcg/kg/day.
    - Monitor CBCs for Dosage Adjustments: During the initial 4 weeks of therapy and during the 2 weeks following and dosage adjustment, monitor CBCs with differential and platelet counts. Once a patient is clinically stable, monitor CBCs with differential and platelet counts monthly during the first year of treatment. Thereafter, if clinically stable, less frequent routing monitoring is recommended.

Special Populations (Adults)

	Comments
Elderly	Of 855 patients enrolled in clinical trials, 232 were age 65 or older and 22 were greater than 75. No overall differences in safety or effectiveness in these subjects compared to younger patients.
Pregnancy	Pregnancy Category C. No adequate or well-controlled studies in pregnant women. The potential risk to the fetus is unknown. Case reports of transplacental passage of filgrastim products when administered ≤30 hours prior to preterm delivery (≤30 weeks gestation). Use during pregnancy only of potential benefit justifies potential risk. No malformations observed when administered in other species. In pregnant rabbits, reduced embryo-fetal survival and increased abortions were observed. No maternal or fetal effects seen in pregnant rats.
Lactation	It is unknown if filgrastim products are excreted in milk. Because many drugs are excreted in human milk, caution should be exercised if filgrastim-sndz is administered to women who are breastfeeding.

Renal Impairment	No Data.
Hepatic Impairment	No Data.
Pharmacogenetics/genomics	No Data.

Projected Place in Therapy

- Filgrastim-sndz has been shown to be biosimilar to the reference filgrastim product in the U.S. and the comparator product in the EU via a totality-of-the-evidence as directed by the FDA biosimilar pathway.
- Because filgrastim is primarily used episodically, that is for 3-14 days for each chemotherapy cycle with exceptions for post bone marrow transplant and chronic neutropenia syndromes, use of different white blood cell products with each episode may not be problematic.
- Given that in the U.S. we now have 3 C-CSF products to choose from: filgrastim (Neupogen- reference), tbo-filgrastim (Granix- not interchangeable), and filgrastim-sndz (Zarxio-biosimilar to Neupogen and not interchangeable), it would make sense to choose one product as our workhorse agent based on cost.
- Because there may be patient specific situations where one product may be preferred, for example dosing flexibility with vials vs pre-filled syringes or latex allergies, products other than the workhorse will still need to be available.
- During times when the workhorse agent is unavailable, due to raw material shortages or other reasons, it should be safe to administer one of the other G-CSF products.

References

[1] Holzmann J, Balser S, Windisch J. Totality of the evidence at work: the first U.S. biosimilar. Exp Opin Biol Therapy 2016;16:137-142.
[2] Sorgel F, Schwebig A, Holzmann J, et al. Comparability of biosimilar filgrastim with originator filgrastim: protein characterization, pharmacodynamics, and pharmacokinetics. BioDrugs 2015;29:123-131.
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[4] Weise M, Kurki P, Wolff-Holz E, et al. Biosimilars: the science of extrapolation. Blood 2014;124:3191-3196.
[5] Gascon P, Fuhr U, Sorgel F, et al. Development of a new G-CSF product based on biosimilarity assessment. Ann Oncol 2010;21:1419-1429.
[6] Gascon P, Tesch H, Verpoort K, et al. Clinical experience with Zarzio in Europe: what have we learned? Support Care Cancer 2013;21:2925-2932.
[7] Tharmarajah S, Mohammed A, Bagalagel A, et al. Clinical efficacy and safety of Zarzio (EP2006), a biosimilar recombinant human granulocyte colony-stimulating factor. Biosimilars 2014;1:1-9.
[8] Zarxio [package insert]. Sandoz Inc., Princeton, NJ, March 2015.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.