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RISK-BENEFIT ASSESSMENT IN A COHORT OF NEW DRUG APPLICATIONS

Coleen Klasmeier
Torrey Cope[1]

Recent legislation requires the FDA to establish a structured framework for the regulatory assessment of the benefits and risks of new drugs. To determine whether agency reviewers had already begun embodying such a framework in their approval decisions, we examined action packages for the 19 NDAs approved August 1, 2011-July 31, 2012. We found that only eleven of the Office Director memoranda for the reviewed NDAs included explicit risk-benefit assessments, and only one used the "benefit-risk assessment framework" under discussion at FDA. With respect to the factors that reviewers use to guide their risk-benefit determinations, we found that some reviews included relatively straightforward consideration of disease severity and available therapy. In many cases, reviewers consulted competing drugs as reference points for risk and benefit assessments. In two cases, reviewers defined clinical benefit broadly, for example by factoring in the potential for use of the drug to reduce health care costs associated with negative outcomes of the indicated disease state.

FDA is the nation's premiere public health agency. It regulates a substantial proportion of products distributed in the United States and virtually all health care products used in the diagnosis and treatment of disease. Because those products touch on the well-being of the American people in important ways, the agency's approach to regulation is often the subject of close scrutiny. An issue of continued debate concerns the ways in which FDA officials reach conclusions as to the safety and efficacy of products submitted for premarket review. Indeed, of all the activities within the scope of FDA's responsibility, perhaps nothing is regarded by the American public and their representatives in Congress as quite so important as the agency's administration of the new drug approval process.

FDA regulates new drugs primarily by examining their safety and efficacy in the context of premarket review. The key elements of the New Drug Application (NDA) review process are as follows:

- Submission of the NDA, which must contain both efficacy data and safety information.
- FDA's scientific review of the efficacy data and the information about the risks of the product.
- FDA regulatory assessment of the risks relative to the clinical benefits of the product.

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[1] Ms. Klasmeier is Global Coordinator, Food, Drug and Medical Device Regulatory Practice Area Team, and Mr. Cope is an associate at the law firm Sidley Austin LLP in Washington, DC. The views expressed herein are solely those of the authors and do not necessarily reflect the views of Sidley Austin LLP or any of its clients. The authors thank legal assistant Liisi Vanaselja and former summer associate Ryan Kaat for their assistance in connection with the research for this article.

Reduced to its essence, this process entails both a scientific review and, ultimately, the agency's own judgment regarding the degree to which risks are tolerable given the drug's benefits.

Little law exists to guide the regulatory assessment of risk relative to benefit. The primary statutory provision requires only that a new drug be "effective" and "safe" for use under the conditions prescribed, recommended, or suggested in labeling, though the statute does include evidentiary standards for FDA to use in determining whether an application includes enough and the right kind of information on each of those two criteria.[2]

Statutory Safety Standard	Statutory Efficacy Standard
If [FDA] . . . finds . . . that	
(1) the investigations, reports of which are required to be submitted [in the NDA], do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; **. . .** (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions;	(5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof;
[then FDA] shall issue an order refusing to approve the application.	

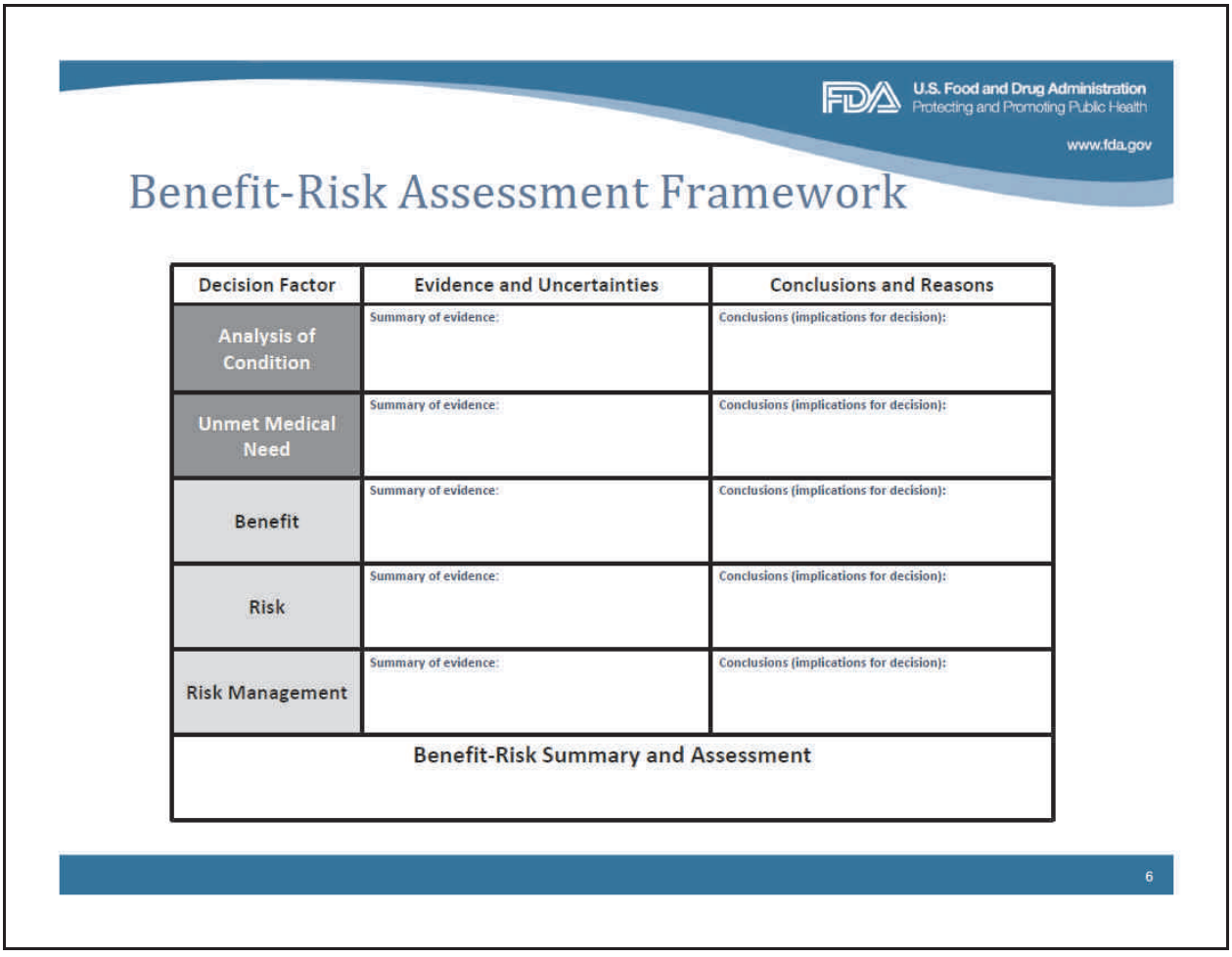
The operative statute and regulations do not articulate standards for FDA to apply in evaluating benefits *in view of* product safety concerns, however.[3] In commentary, FDA has stated that approval is appropriate when a drug has an effect that is "clinically meaningful, and of such importance as to outweigh the risks."[4] Precisely how FDA makes that determination is not set forth in the statute or regulations.

FDA's approach has been the subject of discussion among various key stakeholders, and Congress recently amended the principal statutory section governing NDA reviews by adding new language (to which FDA agreed) on risk-benefit analysis. Under one

[2] 21 U.S.C. § 355(d). The judgment is complicated by uncertainties in quantifying risk and benefit—a subject that is outside the scope of this paper.
[3] 21 C.F.R. §§ 314.100, 314.125.
[4] 57 Fed. Reg. 58942, 58944 (Dec. 11, 1992).

provision of the FDA Safety and Innovation Act (FDASIA), FDA will develop a "structured risk-benefit assessment framework," the better to allow regulatory officials to engage in "the balanced consideration of benefits and risks." The "structured . . . framework" must permit "a consistent and systematic approach to the discussion and regulatory decisionmaking[] and the communication of the benefits and risks of new drugs."[5] Leaving undisturbed the substantive standards that are used to evaluate an NDA, this provision appears intended to enhance the rigor of the regulatory process of premarket review without necessarily making it more or less likely that any particular application will be approved.

For several years FDA officials have dedicated agency resources to devising a more explicit analytical framework to guide risk-benefit determinations. In public presentations, the following graphic has been used to illustrate the agency's proposed multi-factorial approach:



A concern arising from the agency's current approach is the possibility that it could fail to improve predictability or, even worse, lead to even less predictability in FDA reviews of new

[5] Pub. L. No. 112-144, § 905, 126 Stat. 993, 1092 (2012).

drugs. If the analytical framework gives individual reviewers unlimited discretion in conducting risk-benefit determinations, then the mere fact that the framework has been made publicly known will not contribute to meaningful improvement in FDA's processes, although increased transparency may encourage support for further FDA reforms by highlighting the arbitrariness of agency decision making.

We have, in prior papers, explored the extent to which the FDA is, as it claims, "flexible" in applying standards of evidentiary support in the NDA context and the need for legislative reform to permit efficacy information to be added to approved product labeling to enhance its clinical relevancy.[6] Here we examine another facet of the NDA process – the approach that FDA officials use in evaluating the risks of new drugs relative to their benefits to determine whether they should be approved for marketing. FDA's risk-benefit determinations have been described as "purely impressionistic and judgmental," incapable of justification "by modeling or other objective criteria."[7] We anticipated that some objective criteria or decisional algorithms would emerge from a review of a selection of NDAs, particularly because FDA officials have been speaking publicly about the need for a more transparent and predictable approach. The purpose of our analysis was to identify criteria that product developers might use in predicting the likelihood of a favorable risk-benefit determination on a future product candidate.

> "Risk tolerance is not something even the best-designed RCTs tell us. To date, it remains a question answered more by judgment than science . . . . [D]uring the last half of the twentieth century, methodologies for synthesizing the information and balancing the 'good' and the 'bad' remained largely unchanged and poorly described. . . . [T]o many, the regulatory 'thought' process still remains a black box."
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> Lumpkin et al., Advancing the Science of Medicines Regulation: The Role of the 21st-Century Medicines Regulator. 92 Clin. Pharm. & Therapeutics 486, 487 (2012).

I. METHOD AND RATIONALE

Our method involved review of publicly available documents from each NDA review for a year's worth of approvals. To satisfy legal requirements, FDA is required to make available for public disclosure, immediately after approval, a summary basis of approval (SBA) document for each NDA. The SBA must contain a summary of the safety and effectiveness data and information evaluated by FDA during the drug approval process. Formerly the SBA was prepared by the applicant, subject to review by the agency. Currently FDA's practice is to satisfy the SBA requirements by posting key documents from the NDA review on the agency's website.[8] We hypothesized that these materials would include a discussion of the risk-benefit determination, and that agency officials involved in NDA reviews would explain the factors they used in deciding that the approved new drug's benefits outweighed its risks. To standardize our

[6] Coleen Klasmeier & Torrey Cope, NDA Approval Under FDCA Section 505(b)(1) Based on Effectiveness Data from One Clinical Trial (Jan. 10, 2012), http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1991427; Coleen Klasmeier, FDA Regulation of Off-Label Promotion: An Answer (Feb. 5, 2012), http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2000329.

[7] Peter Barton Hutt, Richard Merrill, and Lewis Grossman, Food & Drug Law 696 (3d ed. 2007).

[8] 21 C.F.R. § 314.430. In 2007, Congress enacted the FDA Amendments Act, Section 916 of which amends FDCA § 505 by requiring FDA to "publish the action package for approval" of an NDA. Nothing in this provision expressly requires FDA to document the risk-benefit determination in the action package.

analysis, we reviewed the approval letter for each of these NDAs and the review memorandum prepared by the signatory of each letter. Each signatory was either an Office Director or Deputy Office Director, and we refer to their reviews generally as Office Director memoranda.

We focused our analysis on nineteen NDAs approved under Section 505(b)(1) of the FDCA from August 1, 2011 to July 31, 2012. The NDAs covered new drugs for a wide range of conditions, as set forth in the table below and in Appendix 2. The cohort included seven orphan products and three accelerated approvals. Six received priority review. Nine were referred for advisory committee consideration. Six products had received prior complete response letters.

Table 1. NDAs Reviewed

Approval Date	Drug	Disease area
4/06/12	AMYVID (florbetapir f-18)	Alzheimer's disease
6/27/12	BELVIQ (lorcaserin hydrochloride)	Chronic weight management
5/01/12	ELELYSO (taliglucerase alfa)	Type 1 Gaucher disease
1/30/12	ERIVEDGE (vismodegib)	Basal cell carcinoma
10/14/11	FERRIPROX (deferiprone)	Transfusional iron overload
8/25/11	FIRAZYR (icatibant acetate)	Acute hereditary angioedema attacks
1/27/12	INLYTA (axitinib)	Advanced renal cell carcinoma
11/16/11	JAKAFI (ruxolitinib phosphate)	Myelofibrosis
1/31/12	KALYDECO (ivacaftor)	Cystic fibrosis
7/20/12	KYPROLIS (carfilzomib)	Multiple myeloma
6/28/12	MYRBETRIQ (mirabegron)	Overactive bladder
3/27/12	OMONTYS (peginesatide acetate)	Anemia due to CKD
10/21/11	ONFI (clobazam)	Seizures in Lennox-Gastaut syndrome
1/23/12	PICATO (ingenol mebutate)	Actinic keratosis
4/27/12	STENDRA (avanafil)	Erectile dysfunction
7/23/12	TUDORZA PRESSAIR (aclidinium bromide)	Bronchospasm associated with COPD
8/26/11	XALKORI (crizotinib)	Non-small cell lung cancer
8/17/11	ZELBORAF (vemurafenib)	Melanoma
2/10/12	ZIOPTAN (tafluprost)	Open-angle glaucoma or ocular hypertension

II. KEY FINDINGS

- **Half of the Reviewed NDAs Lacked Explicit Risk-Benefit Assessments, and Only One Used the "Benefit-Risk Assessment Framework" Under Discussion at FDA**

Half of the drugs we reviewed had an explicit risk-benefit assessment, the most extensive of which appeared in the Office Director memorandum for mirabegron (MYRBETRIQ). See Appendix 2.

FDA's review of ruxolitinib (JAKAFI) for myelofibrosis included a "benefit-risk assessment framework" in tabular format, similar to the proposed FDA framework discussed above. The five "decision factors" were listed along with related "evidence and uncertainties" and "conclusions and reasons." According to the review memorandum, the drug's benefits were well-established and subject to uncertainties typically affecting newly-approved drugs—persistency of benefit beyond the duration of therapy studied, and toxicity of long-term treatment. On the risk side, the major risk of thrombocytopenia was deemed manageable by dose adjustments, and the memorandum reflected outstanding questions about the potential risks of long-term therapy. The only "decision factors" directly related to the risk-benefit determination itself were the analysis of the disease, and medical need. The brief discussion of those criteria refers to the seriousness and potential fatality of myelofibrosis and lack of both curative therapy for most patients and effective therapy that reduces symptoms. Although the framework set forth in the memorandum, with its "decision factors" and tabular format, was unique among the drugs we reviewed, in substance the risk-benefit assessment resembled others in its focus on the nature of the disease and the degree of unmet need.

Lunesta

Risk-benefit assessments sometimes change over time and differ among agency officials. An example is Lunesta (eszopiclone), approved in 2004 for the treatment of insomnia. In 2003, the FDA medical review team recommended against approval, citing a safety issue suggested by animal studies and supposed study-design inadequacies. The supervisory pharmacologist had resolved the safety issue, but the Director of the Division of Neuropharmological Drug Products determined that the potential risk without "evidence of a benefit of any sort compared to other available treatments" was too great to justify approval. The higher-level office director reached a different conclusion, finding a favorable risk-benefit profile on the same basis as the supervisory pharmacologist but requiring additional analysis of human tumor and adverse event data, a lowered dosage to minimize side effects, a change in trade name to prevent confusion with an existing product, and enhanced labeling.

As noted, for approximately half of the drugs we reviewed, there was no explicit risk-benefit assessment in the Office Director memorandum. In some cases the assessment was implicit, and appeared in the introduction section or (where a drug was referred to an advisory committee) the advisory committee section of the memorandum. For example, the memorandum for ingenol mebutate (PICATO) includes an advisory committee section which states that the drug was not referred to an advisory committee because it "did not raise any significant safety or efficacy issues." Because advisory committee review often includes risk-benefit assessment, it could be inferred from this statement that agency reviewers had concluded the risk-benefit assessment did not present any challenging question. In some cases the risk-benefit discussion in the advisory committee section of the Office Director memorandum is more expansive. For example, for clobazam (ONFI) for seizures associated with Lennox-Gastaut syndrome, the memorandum justified the decision not to refer the drug to an advisory committee by explaining that the drug "belongs to [a] well characterized drug class (benzodiazepines), and the disease for which the drug is indicated (epilepsy) is well-studied, with numerous approved [antiepileptic drugs]. Moreover, the primary efficacy endpoint (seizures) is well understood, and the treatment effect was substantial."

Office Director memoranda often concurred with other regulatory officials' risk-benefit assessments. Indeed, we found no instance in which an Office Director memorandum overruled a decision by a lower-level agency official. (See Lunesta inset.)

- **Some NDAs Included Relatively Straightforward Risk-Benefit Analyses**

Among the drugs we reviewed, ivacaftor (KALYDECO) for the treatment of cystic fibrosis (CF) appeared to present the simplest risk-benefit determination for agency reviewers. According to the Office Director memorandum:

> The efficacy of ivacaftor was demonstrated in two trials, one in children aged 6-11 years and a second in patients greater than 12 years old. Both trials were of 48 weeks duration and demonstrated improvement in lung function (FEV1) which was the primary endpoint. Clinically important secondary endpoints such as delayed time to first pulmonary exacerbation and improvement in weight gain were also demonstrated.
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> Adverse events were generally well-tolerated. Pre-clinical studies revealed dose-related hepatic toxicities in rodents with an adequate margin of safety. Clinical studies did not reveal overt hepatic toxicity, although the trials were small. The sponsor has proposed labeling to monitor hepatic function.
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> . . . [T]here is a small, but real, concern regarding potential for hepatic toxicity. The database is too small . . . to know if this concern is real. However, given the clear benefit, lack of any other therapy that may alter the long-term outcome of CF, and limited exposure to the population . . . , there clearly exists a favorable risk:benefit calculation that allows marketing with adequate clinical monitoring.

The "robust" clinical benefit was evaluated in terms of the FEV1 endpoint in clinical trials, and the lack of data correlating the endpoint to improved survival posed no obstacle to approval. As was often the case, in this NDA the discussion of risk-benefit was not set forth in a separate section of the Office Director memorandum. Consistent with other NDAs in our cohort, ivacaftor appeared to benefit from its specific proposed indication in patients with a particular genetic mutation (G551D mutation in the CF transmembrane conductance regulator gene). The memorandum stated that the risk:benefit determination was "clearly" favorable due to the limited patient population ($n \approx 1200$) and the lack of available therapy to treat the underlying cause of CF. Advisory committee consideration was deemed unnecessary due to the lack of needed outside expertise, the absence of controversial issues, and the modest number of indicated patients.

Deferiprone (FERRIPROX) similarly was the subject of a favorable risk-benefit determination because of a lack of available therapy. The Office Director memorandum justifies the FDA approval decision with reference to the rarity and severity of the indicated disease state, citing both the need for additional treatment options and the narrowness of the labeled indication.

- **In Many Cases, FDA Used Competing Drugs As Reference Points For Risk-Benefit Assessment**

The FDCA and FDA regulations do not require a sponsor to show, as a condition of approval, that a product is effective versus an active control. Nevertheless, it appears that FDA employees involved in NDA review often use existing approved products as a baseline for the examination of clinical benefit in the context of risk. The implication is that a later entrant in a particular class might not be deemed approvable if it is as effective as an existing drug in that class but riskier, or if it is as risky as an existing drug in the class but less effective. This finding has implications for sponsors developing drugs that are not the first in a class. (An alternative approach would be to consider whether the drug is effective versus placebo, and approve it if the risks are acceptable in view of anticipated clinical benefit, taking account of available risk management measures such as labeling.)

Office Director memoranda typically discuss available therapy to explain the risk-benefit assessment. The Office Director memorandum for avanafil (STENDRA) for erectile dysfunction (ED) indicated that the safety profile for the drug compared to that of other drugs in the class of PDE5 inhibitors, whose safety issues are "well known and can be adequately labeled." Because no new safety concerns were identified relative to other PDE5 inhibitors, the drug was not referred to an advisory committee. The memorandum identifies no major issues with the risk-benefit determination given the statistically significant improvement observed in clinical investigations. Indeed, avanafil is one of 10 drugs in our cohort for which the documents we reviewed included no explicit evaluation of risk relative to benefit.

Sometimes, a favorable risk-benefit assessment will be premised on a new drug candidate's mechanism of action and associated risk reduction. According to the Office Director memorandum for mirabegron (MYRBETRIQ) for over-active bladder (OAB), the only approved therapies for OAB, antimuscarinic agents, were associated with side effects such as dry mouth, constipation, and dry eye that "limit use of these agents in some patients." Because the efficacy of mirabegron, though modest, was well-established in three trials and comparable to that of the antimuscarinics, the Deputy Office Director concluded that the drug had a favorable risk-benefit profile. Deferiprone (FERRIPROX) for transfusional iron overload represents another case in which reviewers cited patients' inability to tolerate side effects of available therapies. In that case, the Office Director memorandum observed that the first drug approved for iron chelation had been available since 1968, but "not all patients can tolerate" the drug because of side effects and difficulties associated with administration. Improvement in the method of administration also justified the favorable risk-benefit determination in the NDA for icatibant (FIRAZYR) for acute attacks of hereditary angioedema, with the Office Director memorandum emphasizing self-injection as "an important advancement of the current armamentarium of therapies." The fact that icatibant had not been associated with the anaphylactic reactions linked to other available therapy also contributed to the favorable risk-benefit assessment.

The review of peginesatide (OMONTYS) reflects the agency's approach to new drugs entering an already crowded class. An intravenously and subcutaneously administered synthetic (not biologic) erythropoiesis stimulating agent (ESA) for the treatment of anemia in CKD, peginesatide could have been a challenging candidate for approval given "all-cause mortality and arterial thromboses related in some way to the use of ESAs to raise hemoglobin (Hgb) levels in CKD." Yet the well-characterized nature of these class risks ultimately appears

to have supported approval of peginesatide, because agency reviewers concluded that the drug had a favorable risk-benefit profile on the ground that its risks were "similar to those for the other marketed ESAs including thrombosis (including death) and hypertension." Far from leading FDA to conclude that available therapy was adequate and that no new entrant should be approved for this condition, reviewers considered available therapy a reason to approve the drug because other products' marketing history had established the risk profile of the class. This was the reviewers' conclusion despite the fact that, according to the Office Director memorandum, "peginesatide has not been extensively studied."

The risk-benefit assessment for peginesatide refers to a critical unknown risk that might have derailed the approval but ultimately was addressed through labeling. According to the Office Director memorandum, "The risk benefit [sic] . . . is not known for the treatment of patients with anemia due to CKD who are not receiving dialysis treatment . . . ." Referring to the review memorandum prepared by another FDA official, the Office Director explained that a less frequent dosing regimen for peginesatide—monthly versus biweekly to three times a week for other ESAs—increased the likelihood that the drug would be used "off-label" in patients "who are not on dialysis simply due to convenience." Ultimately, FDA decided to address this issue by requiring language in approved labeling discouraging administration of the drug to non-dialysis patients.

Although not an explicit factor in the NDAs we reviewed, minor differences in formulation appeared to contribute to a favorable risk-benefit determination in several cases. In reviewing peginesatide, the Office Director noted that the drug was a synthetic (not biologic) ESA, potentially implying that some of the risks identified with the class might prove to be less concerning with a product from non-biologically-derived sources. Similarly, the SBA for tafluprost (ZIOPTAN), a prostaglandin analog for the treatment of elevated intraocular pressure in glaucoma or ocular hypertension, notes that the drug is a preservative-free formulation of a drug that has been approved in multiple ex-US jurisdictions and is a member of a well-understood class. Taliglucerase alfa (ELELYSO) for Gaucher disease had the advantage of a distinct formulation advantage relative to available therapy. While approved enzyme replacement therapy drugs were placentally-derived, recombinant, or produced by gene activation technology in a human fibroblast cell line, taliglucerase alfa is expressed in genetically modified carrot plant root cells in a disposable bioreactor system and therefore "has the advantage that growth media is devoid of serum or any other mammalian-derived products." At the same time, it did not raise "significant safety or efficacy issues that were unexpected for a drug in this class" and did not require advisory committee review.

- **In Some Cases, FDA Defined Clinical Benefit Broadly**

Lorcaserin (BELVIQ) provides an especially useful vehicle for evaluating FDA's approach to risk-benefit determinations. Because of prior regulatory experience with weight-loss drugs, FDA has generally been regarded as reluctant to approve such drugs when there has been any question about the product's safety profile. A key factor in FDA's approach to these products is the assumption that non-drug interventions such as diet and exercise may yield clinically meaningful benefits without drug-related risks. FDA action on BELVIQ was highly anticipated because its potential clinical benefit as a weight-loss drug would reveal agency risk aversion and test the agency's commitment to using risk management measures as a means of facilitating access to new therapies rather than declining approval.

The Office Director memorandum lacks a separate discussion expressly dedicated to the risk-benefit determination, but several themes emerge from the document as a whole. First is the assumption that even modest reductions in weight among patients treated with the drug would reduce adverse outcomes and their associated costs to the health care system. Second is the conviction that no drug with modest efficacy in weight management should be approved unless "off-target" effects are ruled out. The memorandum thus recounts the agency's prior experience with fenfluramine and sibutramine, and emphasizes that "there is little tolerance for potential devastating adverse effects, even if rare," even though "we have a great desire to try to find effective medications for weight management" because of the "myriad of [sic] adverse health outcomes that greatly impact obese people's lives and quality of life while also creating great cost to the health care system."

As with other drugs we reviewed, in considering the application for lorcaserin, agency reviewers assessed benefit by comparison to other drug products. FDA officials concluded that the drug's modest efficacy was acceptable on the ground that it was comparable to the efficacy of other drugs having the same indication, with the memorandum noting that "a small proportion of patients may achieve impressive and probably quite important weight loss." The Office Director's evaluation was also aided by the existence of a draft guidance document establishing "efficacy benchmarks" for clinical trials of weight management drugs. Risks were considered in terms of the "off-target" effects seen with fenfluramine and sibutramine, and the Office Director memorandum concluded that cardiovascular risks in particular were acceptable according to the "same approach that was applied to pending agents used in the treatment of Type-2 DM [diabetes mellitus]." Rather than consider risks and benefits in the abstract, the memorandum used draft guidance as benchmarks and compared risks and benefits to drugs in the same therapeutic category to determine whether the product should be approved.

A final theme in the memorandum worth noting involves considerations of cost. Agency officials' analysis of benefit for lorcaserin included a relatively wide range of treatment advantages—reduction in adverse obesity-related outcomes (as noted above) primarily. But the memorandum also included more than one reference to the costs to the health care system of treating obese patients because of the complexity of those outcomes. The memorandum, in its introductory section, noted that obesity leads to adverse outcomes that "creat[e] great cost to the health care system." And, in responding to the advisory committee meeting suggestion (by one member) that all patients taking lorcaserin be given initial and yearly echocardiograms to manage cardiovascular risks, the memorandum stated: "I do not agree with this approach as it does not protect individual patients, would have a tremendous cost to the health care system, and would not be as instructive as information obtained from planned safety trials."

A relatively novel risk-benefit assessment occurred in FDA's review of the NDA for axitinib (INLYTA) for the treatment of patients with advanced renal cell carcinoma. As the Office Director memorandum states, since 2005 six drugs have been approved for advanced, inoperable renal cell cancer, including sorafenib. These approvals were based on improvement in progression-free survival (PFS), except that temsirolimus was approved based on an overall survival (OS) endpoint in patients with pre-specified poor prognosis risk factors. The development program for axitinib included an international, randomized, open-label trial in patients with advanced renal cell carcinoma after failure of one prior systemic regimen using PFS as the primary efficacy endpoint. The PFS analysis demonstrated a statistically significant

improvement in PFS relative to sorafenib with no difference in the final OS analysis between the two arms.

One factor in particular appeared to contribute to the approval decision. The Office Director memorandum reflected a relatively flexible approach to the assessment of benefit. The trial design provided for enrollment of patients with advanced renal cell carcinoma after failure of one prior systemic regimen that included sunitinib, temsirolimus, bevacizumab, or cytokine(s). Subjects were assigned to receive either axitinib 5 mg orally twice daily or sorafenib 400 mg orally twice daily. Because the treatment effect of a second-line therapy (as in the trial) is not known, the Office Director memorandum concluded that the efficacy of axitinib should be calculated based not only on the axitinib PFS benefit from the open-label trial, but also on the treatment effect of sorafenib. Although axitinib's improvement in PFS was "modest" compared with sorafenib, axitinib had a favorable risk-benefit profile because of the agency reviewers' flexible approach to the calculation of benefit and the safety of axitinib was deemed comparable to that of other drugs in the same class.

III. CONCLUSIONS AND LIMITATIONS

We found that an explicit risk-benefit assessment framework was available in only one Office Director memorandum among the 19 drugs we reviewed. An explicit risk-benefit assessment was included in the Office Director memoranda for only about half of the drugs. Some drugs we reviewed had risk-benefit determinations involving relatively straightforward consideration of well-characterized clinical benefit and risk, contextualized by analysis of disease severity and available therapy. In many cases, reviewers used available therapy as a basis of comparison for risk and benefit. FDA reviewers sometimes calculated the benefits of a new drug by including extrinsic factors, such as the benefits of another drug as determined in an active-control trial (INLYTA) or the savings to the health care system associated with reduction in adverse outcomes (BELVIQ). The result was a more favorable risk-benefit assessment.

Important limitations affected the review of NDAs described in this paper. First, risk-benefit assessment might be reflected in sources that were not included in our analysis. This could include, among other sources, the approved physician labeling, documents included in the SBA or action package other than the Office Director memorandum, documents prepared by FDA to support advisory committee consideration, and documents not included in the SBA or action package. In some recent cases, FDA officials have even relied on the published medical literature to explain the reasoning behind a drug approval decision.[9] Second, we did not include NDAs that were acted upon during this period but did not receive approval. Our analysis therefore does not include drugs that FDA decided did not have a favorable risk-benefit ratio. Third, we analyzed only NDAs approved under Section 505(b)(1) of the FDCA. Drugs approved under Section 505(b)(2) present potentially different risk-benefit considerations. Finally, a more complete picture of FDA's risk-benefit determinations could emerge from a review of a greater number of NDAs or a cohort selected to be representative across review divisions, therapeutic areas, or pharmacologic or therapeutic drug classes. Such a review could be a useful subject of further inquiry.

[9] See, e.g., Eric Colman et al., The FDA's Assessment of Two Drugs for Chronic Weight Management, 367 NEJM 1577 (2012).

APPENDIX 1: OFFICE DIRECTOR MEMORANDA REVIEWED

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
AMYVID (florbetapir f-18) Avid Standard	4/6/2012 (complete response 3/17/2011)	Peripheral and Central Nervous System Drugs Advisory Committee (1/20/2011): 3 yes, 13 no	Director, Office of Drug Evaluation IV	None	Amyvid is indicated for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline. A negative Amyvid scan indicates sparse to no neuritic plaques and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD, but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition. Amyvid is an adjunct to other diagnostic evaluations. Limitations of Use: • A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder. • Safety and effectiveness of Amyvid have not been established for: • Predicting development of

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
					dementia or other neurologic condition; • Monitoring responses to therapies.
BELVIQ (lorcaserin hydrochloride) Arena Standard	6/27/2012 (complete response 10/22/2010)	Endocrinologic and Metabolic Drugs Advisory Committee (9/16/2010): 5 yes, 9 no Endocrinologic and Metabolic Drugs Advisory Committee (5/10/2012): 18 yes, 4 no, 1 abstain	Director, Office of Drug Evaluation II	None	BELVIQ is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of: • 30 kg/m2 or greater (obese), or • 27 kg/m2 or greater (overweight) in the presence of at least one weight related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes) <u>Limitations of Use</u>: • The safety and efficacy of coadministration of BELVIQ with other products intended for weight loss including prescription drugs (e.g., phentermine), over-the-counter drugs, and herbal preparations have not been established • The effect of BELVIQ on cardiovascular morbidity and mortality has not been established
ELELYSO (taliglucerase	5/1/2012 (complete response 2/24/2011)	N/A	Director, Office of Drug	None	ELELYSO (taliglucerase alfa) for injection is a hydrolytic lysosomal glucocerebroside-specific enzyme

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
alfa) Protalix Standard Orphan			Evaluation III		indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease.
ERIVEDGE (vismodegib) Genentech Priority	1/30/2012	N/A	Director, Office of Hematology and Oncology Products	"The benefits of ERIVEDGE outweigh its risks in this patient population, for whom there is no FDA-approved treatment for metastatic disease or where FDA-approved local therapy (imiquimod or 5FU cream) has not been adequately studied. Regular approval should be granted for this application based on the long duration of responses, which provide both cosmetic improvement as well as the potential for symptomatic relief, in a population with a serious and potentially life-threatening disease. "The toxicity profile of this product is dominated by mild to moderate muscle spasms, fatigue, and weight loss, as well as alopecia in most patients, however these toxicities led to termination of treatment in a small fraction of the patients, primarily those with localized disease. The major risk is to the fetus of a woman exposed to ERIVEDGE during pregnancy. As discussed below, this risk can be	ERIVEDGE capsule is indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				minimized through contraception (females) and barriers (males); this risk is common to other antineoplastic agents has been generally well-managed by medical oncology community through education of patients and contraceptive use. These risks do not outweigh the benefits of durable tumor shrinkage in the indicated patient population. "The risk-benefit profile was also assessed in the Division Director, CDTL and clinical review, and I concur with their assessment as well as their (and review team's) recommendation to approve this application."	
FERRIPROX (deferiprone) ApoPharma Standard Orphan Accelerated	10/14/2011 (complete response 11/30/2009)	Oncologic Drugs Advisory Committee (9/14/2011): 10 yes, 2 no	Director, Office of Hematology and Oncology Products	"The risk benefit assessment suggests that oral deferiprone is effective for the treatment of patients with transfusional iron overload due to thalassemia syndromes who have had an inadequate response to available iron chelator therapy. The primary endpoint was serum ferritin, a surrogate endpoint that is reasonably likely to predict clinical benefit. This approval will be subject to the requirement that the applicant study the product further, to verify and describe its clinical benefit. The most	FERRIPROX® (deferiprone) is indicated for the treatment of patients with transfusional iron overload due to thalassemia syndromes when current chelation therapy is inadequate. Approval is based on a reduction in serum ferritin levels. There are no controlled trials demonstrating a direct treatment benefit, such as improvement in disease-related symptoms, functioning, or increased survival.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				serious side effect is agranulocytosis. The most common side effects include: gastrointestinal specifically nausea, vomiting, and arthropathy."	Limitation of Use: • Safety and effectiveness have not been established for the treatment of transfusional iron overload in patients with other chronic anemias.
FIRAZYR (icatibant acetate) Shire Priority Orphan	8/25/2011 (complete response 4/23/2008)	Pulmonary-Allergy Drugs Advisory Committee (6/23/2011): 12 yes, 1 no	Director, Office of Drug Evaluation II	None	FIRAZYR® (icatibant) is indicated for the treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.
INLYTA (axitinib) Pfizer Standard	01/27/2012	Oncologic Drug Advisory Committee (12/7/2011): 13 yes, 0 no	Director, Office of Hematology and Oncology Products	"A modest improvement in PFS was demonstrated with the use of axitinib compared to sorafenib. Sorafenib is commonly used to treat renal cell cancer; however, its treatment effect as a second-line treatment is not known. The treatment effect of sorafenib should be added to the axitinib PFS benefit to give the total treatment effect of axitinib. In addition, axitinib has a different but generally manageable toxicity profile when compared to other recently approved agents for renal cell cancer. The risk:benefit profile has also been assessed by the Deputy Division Director, CDTL and clinical reviewer,	INLYTA is indicated for the treatment of advanced renal cell carcinoma (RCC) after failure of one prior systemic therapy.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				and I concur with their recommendation, as well as other discipline reviewer recommendations to approve this application."	
JAKAFI (ruxolitinib phosphate) Incyte Priority Orphan	11/16/2011	N/A	Director, Office of Hematology and Oncology Products	"MF is a serious, life-threatening condition in which death is due to evolution into AML (12%), bleeding (1%), portal hypertension (7%), and liver insufficiency (9%). For most patients, there is no curative therapy, and no effective treatment which reduces symptoms and splenomegaly for a long time. There is an unmet medical need in MF. Two large well controlled and well designed trials met efficacy endpoints when measured at 24 and 48 weeks of therapy. Uncertain is the how long [sic] benefits will last beyond the 24 and 48 weeks and what will be the toxicity of long-term treatment. Thrombocytopenia was successfully managed by a dose adjustment schedule. Anemia was managed by RBC transfusions. The risks of long term therapy have not been characterized. PMR for follow-up (for 3 years after randomization) of phase III trial populations for myelosuppression. PMC for post-marketing follow-up of efficacy and	Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				safety outcomes of current randomized trials and to report on discontinuation of at least 150 patients previously entered onto the randomized trials to determine if specific cautions are appropriate to describe discontinuation strategies. "The benefits and risks of ruxolitinib were also discussed in the Division Director's Summary Review and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. This application is supported by the results of two well designed, well controlled, randomized trials of ruxolitinib in patients with MR demonstrating a clinically significant benefit with ruxolitinib. The major side effect of thrombocytopenia can be limited by dose adjustments."	
KALYDECO (ivacaftor) Vertex Priority	1/31/2012	N/A	Director, Office of Drug Evaluation II	None	KALYDECO is classified as a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator. KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who have a G551D mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
					the presence of the G551D mutation. Limitations of Use: KALYDECO is not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene and has not been studied in other populations of patients with CF.
KYPROLIS (carfilzomib) Onyx Standard Accelerated	7/20/2012	Oncologic Drugs Advisory Committee (6/20/2012): 11 yes, 1 abstain	Director, Office of Hematology and Oncology Products	"The risk benefit assessment suggests that carfilzomib is effective for the treatment of patients with multiple myeloma whose disease has relapsed after receiving established and approved treatments such as bortezomib, lenalidomide, thalidomide, mephalan and other alkylating agents. The most common side effects include: fatigue, anemia, nausea, thrombocytopenia, dyspnea, diarrhea, and pyrexia. The following adverse reactions were identified as being particularly concerning: cardiac, pulmonary, hepatic, thrombocytopenia, and infusion reactions. The latter list is included in the warnings and precautions section of the labeling. Additionally the cardiac and pulmonary will be the subject of ongoing PMRs under FDAAA. The risk-benefit profile was also assessed by the clinical review team and Dr. Farrell, and I concur	KYPROLIS is indicated for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				with their recommendations to approve this application."	
MYRBETRIQ (mirabegron) Astellas Standard	6/28/2012	Advisory Committee for Reproductive Health Drugs (4/5/2012): 7 yes, 4 no, 1 abstain	Deputy Director, Office of Drug Evaluation III	"The only currently available approved therapies for the treatment of OAB are the antimuscarinic agents. These agents have modest efficacy, having shown an approximate 8-9% increase in the number of patients experiencing either a modest decrease in the number of micrtitions/24 hours (0.8) or a decrease in the number of incontinence episodes/24 hours (0.7) as compared to placebo. The side effects associated with antimuscarinic agents are well described and include dry mouth, constipation, blurred vision, dry eyes and urinary retention. These side effects limit use of these agents in some patients. "Mirabegron is an NME with a unique mechanism of action as compared to that of currently available therapies for OAB . . . . [E]fficacy . . . is similar to that seen with the antimuscarinics. . . . "A majority of the Advisory Committee members agreed that mirabegron was safe and effective for the treatment of OAB and that the risk benefit assessment supported approval.	Myrbetriq is a beta-3 adrenergic agonist indicated for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				Although the efficacy effect is modest, it is similar to that seen with the antimuscarinics. Additionally, because it does not have the anticholinergic side effects associated with the antimuscarinics mirabegron may provide an alternative therapy for patients who cannot tolerate the currently available therapy."	
OMONTYS (peginesatide acetate) Affymax Standard	3/27/2012	Oncologic Drug Advisory Committee (12/7/2011): 15 yes, 1 no, 1 abstain	Director, Office of Hematology and Oncology Products	"The risk benefit assessment suggests that peginesatide is effective for the treatment of patients with anemia due to CKD who are receiving dialysis. The risk benefit of the use of peginesatide is not known for the treatment of patients with anemia due to CKD who are not receiving dialysis treatment and therefore this will be a limitation of use. Safety risks are similar to those for the other marketed ESAs including thrombosis (including death) and hypertension. The safety and effectiveness of pegiinesatide in the treatment of anemia due to cancer chemotherapy is not known; therefore, there will be a limitation of use to communicate a recommendation not to use. The risk-benefit profile was also discussed in the reviews by Drs. Farrell, Robie-Suh and Dmytrijuk, and I concur with their	OMONTYS® is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis. <u>Limitations of Use</u>: OMONTYS is not indicated and is not recommended for use: • In patients with CKD not on dialysis because of safety concerns in this population. • In patients receiving treatment for cancer and whose anemia is not due to CKD, because ESAs have shown harm in some settings and the benefit-risk factors for OMONTYS in this setting have not been evaluated. • As a substitute for RBC transfusions in patients who require immediate correction of anemia.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				assessment as well as the review team's recommendation for approval."	• OMONTYS has not been shown to improve symptoms, physical functioning or health-related quality of life.
ONFI (clobazam) Lundbeck Standard Orphan	10/21/2011	N/A	Deputy Director, Office of Drug Evaluation I	None	ONFITM (clobazam) is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.
PICATO (ingenol mebutate) Leo Standard	1/23/2012	N/A	Deputy Director, Office of Drug Evaluation III	None	Picato® gel is indicated for the topical treatment of actinic keratosis.
STENDRA (avanafil) Vivus Standard	4/27/2012	N/A	Deputy Director, Office of Drug Evaluation III	None	STENDRA is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of erectile dysfunction.
TUDORZA PRESSAIR (aclidinium bromide) Forest	7/23/2012	Pulmonary-Allergy Drugs Advisory Committee (2/23/2012): 12 yes, 2 no	Director, Office of Drug Evaluation II	None	TUDORZA™ PRESSAIR™ (aclidinium bromide inhalation powder) is indicated for the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
Standard					and emphysema.
XALKORI (crizotinib) Pfizer Priority Orphan Accelerated	8/26/2011	N/A	Director, Office of Oncology Drug Products	"Compared to conventional chemotherapy, there was a marked elevation in response rate and duration of response observed in two single-arm studies with crizotinib. It is thought that this will translate into an improvement in overall survival in this patient population; however, as a condition of accelerated approval, two Phase 3, randomized (crizotinib vs. conventional chemotherapy) confirmatory trials are required to be conducted by the applicant to verify clinical benefit. "Although crizotinib appears to be less toxic than conventional chemotherapy, further follow up and examination of the adverse event profile of crizotinib in a randomized trial will be necessary to fully define the safety signals associated with crizotinib. "The benefits and risks of crizotinib were discussed in the Division Director's Summary Review, the CDTL and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. In conclusion, I concur with the review	XALKORI is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test. This indication is based on response rate. There are no data available demonstrating improvement in patient reported outcomes or survival with XALKORI.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
				team's recommendation for approval."	
ZELBORAF (vemurafenib) Hoffman-LaRoche Priority Orphan	8/17/2011	N/A	Director, Office of Oncology Drug Products	"Until the approval of ipilimumab earlier this year, no treatment had been shown to improve overall survival in advanced malignant melanoma. Although the median survival has not yet been reached for vemurafenib in the randomized study, the overall survival in the vemurafenib arm is clearly superior to that in the dacarbazine arm. Additional follow-up will provide a better estimate of the survival with vemurafenib treatment. The improvement in survival is supported by clinically and statistically significant improvements in progression-free survival and objective response rate. The toxicity profile is better than that of most cytotoxic chemotherapeutic agents and is clearly acceptable for a disease that has a dismal prognosis. "The benefits and risks of vemurafenib were discussed in the Division Director's Summary Review, the CDTL and Clinical Reviews. The review team found the risk-benefit assessment to be acceptable. In conclusion, I concur with the review team's recommendation for approval."	ZELBORAF is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test. Limitation of Use: ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma.

Drug Sponsor Review Type	Approval Date	Advisory Committee Vote	Signatory Authority	Explicit Risk-Benefit Discussion in Office Director Memorandum	Indication on Approval
ZIOPTAN (tafluprost) Merck Sharpe & Dohme Standard	2/10/2012 (complete response 11/7/2011)	N/A	Director, Office of Antimicrobial Products	None	ZIOPTAN (tafluprost ophthalmic solution) 0.0015% is indicated for reducing elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

APPENDIX 2: DRUG-SPECIFIC NOTES

AMYVID (florbetapir f-18)

The first-cycle review resulted in an Advisory Committee vote against approval and a March 2011 Complete Response action letter for this radioactive diagnostic agent for positron emission tomography (PET), used in the diagnosis of Alzheimer's disease. The key deficiency in the original application related to the ability of practitioners to interpret PET scan results without adequate training, because the practitioners who read all of the scans in the original trials had extensive face-to-face training. The action letter requested development of clinically applicable training materials and a study to verify establish the validity of the training.

The sponsor's response to the action letter was submitted in October 2011, and included the results of a study that evaluated the adequacy of a compact-disc (CD) based training. There was no explicit risk-benefit assessment in the Office Director memorandum, but it did include discussion of whether training by the sponsor should be required:

> There were a variety of opinions expressed including that no training by the sponsor should be required. After much internal discussion, it was decided that the training should not be mandatory but should be recommended in the labeling. There was concern that making it mandatory, such as face to face training or even through various e-methods (web-based, compact disc), would be cumbersome to require and track. This was also unprecedented, in that, other imaging applications, where in some cases the scans are difficult to read, we have not required a sponsor to develop a training program. The sponsor developed a training program and validated its ability to train readers (although we acknowledge there is no baseline with which to compare) resulting in an acceptable sensitivity and specificity. We have described the content of the training program in the labeling rather than treat the content as a separate entity. The following language is included in the labeling: *Amyvid images should be interpreted only by readers who successfully complete a special training program. Training is provided by the manufacturer using either an in-person tutorial or an electronic process.*

BELVIQ (lorcaserin hydrochloride)

The first-cycle review resulted in an October 2010 Complete Response for this weight-loss drug. The action letter emphasized breast and brain tumor findings in animal studies, which were very concerning in the context of fairly "marginal" evidence of efficacy. The letter requested additional evidence and analysis regarding these findings, and noted that additional clinical studies "may be required to obtain a more robust assessment of lorcarserin's benefit-to-risk profile."

Other important issues related to potential for valvular heart disease (VHD) and cardiovascular events. VHD was a concern because another weight-loss drug, fenfluramine, was withdrawn from the market after it became associated with primary pulmonary hypertension and valvular regurgitation. Withdrawal had been necessary for fenfluramine because "[t]his

adverse event profile, in the context of fairly marginal weight loss and inability to identify those that may be at risk, was deemed too unsafe to allow continued marketing."

Cardiovascular (CV) risks were also a concern because patients with obesity have greater baseline cardiovascular risks than the general population, and because the weight-loss drug sibutramine had been withdrawn from the market after it became associated with cardiovascular harm. As with fenfluramine, "a population could not be identified where weight loss with sibutramine was significant enough to overcome the risk."

The Office Director memorandum acknowledged, however that it is not "feasible" to obtain definitive data regarding cardiovascular risk before approval, or even "practical" to obtain such data in any randomized trial, because large trials would need to be conducted for long periods of time. Thus, FDA used a "two-step" approach to risk assessment, by allowing approval based on studies that rule out a certain degree of risk, and then requiring a longer and larger outcome study after approval to rule out a lower degree of risk. In the case of BELVIQ, FDA determined that marketing could be justified based on studies that ruled out a two-fold increase in risk, given the relatively high background rates of cardiovascular events in the obesity population and the difficulty of ruling out a smaller increase in risk before approval. The memorandum noted that this is similar to the approach taken to cardiovascular risk for drugs that treat Type 2 diabetes mellitus, but that FDA had "not yet made a formal policy decision upon the requirements necessary for CV evaluation of obesity drugs."[10]

The sponsor submitted a response to the action letter in December 2011, which included additional data and analysis regarding the pre-clinical carcinogenicity findings, the potential for clinically important VHD, and the potential for cardiovascular risks. There was no express risk-benefit assessment for BELVIQ, but the Office Director memorandum noted that "there is little tolerance for potential devastating adverse effects, even if rare, in the environment of modest weight loss." On the other hand, the memorandum acknowledged "the urgency to try to provide aid and appropriate treatments" for obesity, and "the lack of effective therapies as was emotionally and movingly voiced during the open public session [of an advisory committee meeting] by many suffering from obesity."

The memorandum noted that efficacy was "not impressive," with placebo-subtracted mean differences in weight loss of 3.7% in one trial and 3.0% for another, but approval was granted because this was "not out of line with other weight loss drugs," and because the sponsor's data and analysis had adequately addressed all of the relevant risks. A post-approval trial to further evaluate cardiovascular outcomes was also required.

ELELYSO (taliglucerase alfa)

The first-cycle review resulted in a February 2011 Complete Response action letter for this enzyme replacement therapy (ERT) product for patients with Gaucher disease. The action letter primarily cited issues relating to product quality and assays used to measure anti-product and neutralizing antibodies, but also some issues relating to clinical evidence of efficacy and safety. The original NDA submission relied primarily on data from a single, 9-

[10] See FDA, Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (Dec. 2008).

month clinical trial in 32 patients. The action letter noted that these data were insufficient for assessment of efficacy and safety in patients switched from other ERT products, and for assessment of longer-term safety.

The sponsor's response to the action letter was submitted in August 2011, and the second-cycle review resulted in approval. The Office Director memorandum did not include an explicit risk-benefit assessment, but did discuss the efficacy results of the original trial and another 9-month trial in 28 patents switched from another ERT product. For longer-term safety, the memorandum noted that safety was assessed in a total of 121 patients, 59 of whom had received the product for 12 months. The most serious risks were severe allergic reactions (including anaphylaxis) and infusion reactions. The memorandum noted some remaining immunogenicity issues, and that additional assay development and studies were needed to characterize the effect of anti-product and neutralizing antibodies, but none of these were deemed serious enough to preclude approval.

ERIVEDGE (vismodegib)

Efficacy was demonstrated in one, single-arm clinical trial in 104 patients with metastatic or locally advanced basal cell carcinoma (BCC). The risk-benefit assessment emphasized that this is a serious and potentially life-threatening disease, for which there are no FDA-approved treatments. Patients in the trial experienced durable tumor shrinkage, which provided both cosmetic improvement and a potential for symptomatic relief.

The primary safety issue related to teratogenicity. There were no human data on effects of the drug on fetal development, but the drug was teratogenic, embryotoxic, and fetotoxic in animal studies. Evidence of risk also came from findings related to other drugs in the class, and the established relationship between the drug's mechanism of action and embryofetal development.

The risk-benefit assessment concluded that this risk could be adequately managed by oncologists who will use the drug, and that a Risk Evaluation and Mitigation Strategy (REMS) was not necessary, because the risk is "common to other antineoplastic agents and has been generally well-managed by [the] medical oncology community through education of patients and contraceptive use." The approval letter also required a pregnancy pharmacovigilance study to assess this risk.

FERRIPROX (deferiprone)

The first-cycle review resulted in a November 2009 Complete Response action letter for this iron chelator that treats transfusional iron overload due to thalassemia syndromes. The original NDA sought accelerated approval on the basis of a single clinical trial that measured a surrogate endpoint, cardiac content of iron, with magnetic resonance imaging (MRI). The NDA also sought approval in all patients with excessive iron due to chronic transfusion therapy.

The action letter was highly critical of the trial, and concluded that it did not provide adequate information to establish that the drug is safe and effective. A key problem related to the use of cardiac MRI to demonstrate efficacy. The sponsor argued that increases in

cardiac MRI measurements are indicative of a decrease in cardiac iron and of clinical benefit. The action letter disagreed, and asserted that the NDA did not adequately establish a specific clinical benefit that could be attributed to the MRI measurements.

In response to the action letter, the sponsor limited the proposed indication to patients for whom currently available chelation therapy is inadequate, and conducted a prospectively designed analysis of data from 12 clinical trials. This analysis showed a positive effect on serum ferritin level, a surrogate endpoint that FDA determined is reasonably likely to predict clinical benefit.

The most serious side effect was agranulocytosis, which was seen in approximately 1.7% of patients treated with FERRIPROX and was associated with some patient deaths. The drug is also genotoxic, carcinogenic, teratogenic, and potentially associated with liver toxicity. The Office Director memorandum noted that the drug should be used only "in a serious disease, when other therapies are considered adequate." The memorandum also concluded that these risks could be adequately addressed with a boxed warning about agranulocytosis, a Medication Guide for patients, and post-approval studies.

Accelerated approval was granted, subject to confirmation of clinical benefit in trials evaluating changes in cardiac and liver iron concentration. The decision was expressly characterized as "consistent with initiatives to provide important flexibility in the approval of drugs that treat rare and serious diseases, in the interest of patients in whom available therapy is inadequate."

FIRAZYR (icatibant acetate)

The first-cycle review resulted in a Not Approvable action letter in April 2008, which cited several deficiencies in the clinical data.

The sponsor sought approval for treatment of acute attacks of hereditary angioedema (HAE), and efficacy was assessed in two trials: one with tranexamic acid as an active control; and one with placebo control. The action letter asserted that these studies did not provide adequate evidence of safety and efficacy because the efficacy of tranexamic acid is uncertain and there was no statistically different treatment difference in the placebo-controlled trial. The letter concluded that, "[w]ithout substantial evidence of the efficacy . . . , we cannot evaluate if there is appropriate safety."

The action letter also noted that data were needed to show that patients can safely self-inject the drug, because it is supplied in a pre-filled syringe and is used in settings outside the usual healthcare delivery environment.

The sponsor's response was submitted February 2011 and included results from a new placebo-controlled trial and a self-injection trial. The placebo-controlled trial showed a robust improvement in time to symptom relief, and the self-injection trial showed that patients can adequately self-inject the drug for perceived attacks. The Office Director memorandum also emphasized that HAE is a rare disease, acute HAE attacks can be life threatening, and other available products require administration by healthcare professionals.

One significant issue in the Office Director memorandum related to the recommendation of the Center for Devices and Radiological Health (CDRH) that the sponsor conduct "human factors" testing of the pre-filled syringe before approval. The point of this testing would be to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. The Office Director concluded that this additional study was not necessary:

> [O]ne could posit that Human Factors testing should be performed prior to actual field testing to be hypothesis generating regarding potential safety problems that may be remediated prior to field testing. In this instance, we have abundant data indicating success with self-injection. To follow CDRH's recommendation seems counter-intuitive, as we have a great deal of actual use, by HAE patients, under real use conditions, and there have not been any patterns of failures emerging with self-administration that need remediation. Therefore, I do not agree that a Human Factors study is relevant or necessary in this situation and believe that the delay in marketing while one is being performed would actually be detrimental to the health of those patients with HAE that do not have ready access to treatment at a center with expertise in this disease.

INLYTA (axitinib)

The risk-benefit assessment was minimal for this sixth-in-class treatment for renal cell carcinoma. A "modest" improvement in progression-free survival (PFS) was demonstrated in a single, randomized, open-label trial. The toxicity profile was described as "different but generally manageable" when compared to other approved agents for renal cell cancer.

JAKAFI (ruxolitinib phosphate)

This was the first of a new class of kinase inhibitors, and the first therapeutic agent shown to decrease splenomegaly and to ameliorate symptoms in myelofibrosis. The Office Director memorandum included a detailed "Benefit-Risk Assessment Framework" chart, taken from the Clinical Review.

The Framework included detailed analysis of the relevant medical condition (i.e., clinical manifestations and prognosis), the available therapy, the clinical benefit and risks of the drug, and relevant risk management measures. For each of these categories, the Framework provided a description of the available evidence, the relevant uncertainties, and the reviewer's conclusions.

The Framework emphasized that myelofibrosis is a serious condition, associated with median survival of 57 months, splenomegaly, and symptoms that disrupt quality of life. There is no curative therapy for most patients, and no FDA-approved treatment for long-term treatment.

Two clinical trials showed reduction of splenic volume and total symptom score at 24 and 48 weeks. The most serious risks included thrombocytopenia and anemia, but these were "successfully" managed with dose adjustment and red blood cell transfusions. The Framework emphasized that long-term benefit and toxicity were not known, and longer-term post-approval studies were necessary to further characterize the drug's long-term benefits and risks. The approval letter did not require such studies, but did describe a post-marketing commitment to provide longer-term efficacy and safety outcomes and 3-year follow up data from trials that were ongoing at the time of approval.

KALYDECO (ivacaftor)

The Office Director memorandum for this first-in-class treatment for cystic fibrosis emphasized a number of factors that made the risk-benefit calculation "clearly" favorable:

- Cystic fibrosis is a serious, debilitating disease that leads to premature mortality. The root cause of the disease relates to diminished function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. Poor CFTR function results in tenacious secretions in the pulmonary and gastrointestinal tracts, causing infection, inflammation, malabsorption of nutrients and poor weight gain, and respiratory failure.

- KALYDECO is the first treatment that directly targets the root cause of cystic fibrosis, by restoring some function of the CFTR protein.

- The clinical trials demonstrated a "robust" improvement in lung function, as well as decreased pulmonary exacerbations and improved weight gain. The memorandum noted that it was premature to know whether KALYDECO will alter the course and outcome of cystic fibrosis, but there was "great potential" for the therapy to be a "game-changer" for some patients based on its "action at the 'root' of the problem."

- The primary safety issue related to dose-related findings of liver toxicity in animal studies. There were no findings consistent with hepatotoxicity in the human trials, but this was not dispositive because the number of trial subjects was small (n=221). Further evaluation before approval was deemed unnecessary "due to the limited population (N≈1200) that will receive this drug," which makes it "unlikely this issue could be further explored or defined before approval. Also, due to the limited population that will receive ivacaftor, there will be limited patients placed at risk should rare events be noted to occur associated with drug use." The approval letter did not require further study relating to this issue.

KYPROLIS (carfilzomib)

The risk-benefit assessment for this accelerated approval referred to a suggested benefit for patients with multiple myeloma who have failed at least two other therapies, based on a trial that measured objective response rate (ORR). The approval letter required confirmation of clinical benefit by a trial demonstrating an improvement in progression-free survival (PFS).

The risk-benefit assessment also noted several "particularly concerning" adverse reactions that were observed in clinical trials, although there trials were not controlled and the lack of a comparator made it "difficult to state with certainty whether the adverse reactions observed are attributable to the drug, underlying (non-myeloma disease), or prior therapy." These reactions were cardiovascular events, hepatotoxicity, pulmonary toxicity, thrombocytopenia, and infusion reactions. The approval letter included requirements for postmarketing studies to evaluate all of these issues, except thrombocytopenia.

According to the section of the Office Director memorandum entitled "Risk Benefit Assessment," the drug is effective for patients with multiple myeloma whose disease has relapsed after receiving established and approved treatments, and several adverse reactions were "particularly concerning," including thrombocytopenia and infusion reactions. The discussion concluded, "The risk-benefit profile was also assessed by the clinical review team and Dr. Farrell, and I concur with their recommendations to approve this application."

MYRBETRIQ (mirabegron)

The detailed risk-benefit assessment for this overactive bladder (OAB) treatment described the efficacy effect as "modest," but similar to that seen with other available treatments.

There were several risks associated with the drug, including dose-related increases in heart rate and blood pressure, neoplasms, and possible hepatotoxicity, but the assessment emphasized that these risks could all be mitigated through: approval of a low dose; labeling that excludes patients with severe hypertension; and further evaluation in post-market studies. The assessment also emphasized the potential for the drug to provide an alternative for patients who could not tolerate the currently available therapy.

OMONTYS (peginesatide acetate)

The risk-benefit assessment for this fourth-in-class erythropoiesis-stimulating agent (ESA) for the treatment of anemia due to chronic kidney disease (CKD) focused on the "major" safety concerns known to be associated with these products. These include increased risks of death, myocardial infarction, stroke, thromboses, and tumor progression when used to treat anemia due to cancer chemotherapy.

The trials for OMONTYS showed that efficacy was non-inferior to other available therapies, both in CKD patients on dialysis and in CKD patients not on dialysis. The safety results were closely scrutinized for both of these populations, however, and suggested that the safety profile could be unfavorable for OMONTYS in non-dialysis patients. In these patients, safety outcomes were numerically worse for OMONTYS. According to the sponsor's pre-specified primary safety analysis plan, the difference was also statistically significant. Using the secondary analysis plan, the differences were not statistically significant.

The Office Director memorandum acknowledged that there were differences in baseline characteristics between the OMONTYS groups and the comparator groups in the non-dialysis trials. But, the memorandum concluded that additional sensitivity and exploratory

analyses did not provide evidence that the imbalance impacted the "overall suggestion" of a higher risk with OMONTYS.

The memorandum concluded that safety risks were similar to other marketed ESAs in dialysis patients, but that risk-benefit is "not known" in non-dialysis patients. The assessment also noted that safety and effectiveness for anemia due to cancer chemotherapy is not known. As a result, the drug's indication was limited to CKD patients on dialysis, and included limitations of use that specifically excluded use in CKD patients who are not on dialysis, and in patients with anemia due to cancer chemotherapy. The approval letter also required further observational and randomized safety studies to assess the potential for increased risk of adverse cardiovascular events.

ONFI (clobazam)

There was no express risk-benefit assessment in the Office Director memorandum for this treatment for seizures associated with Lennox-Gastaut Syndrome (LGS). The memorandum emphasized that LGS is a severe form of child-onset epilepsy, for which there are few treatment options, and that clobazam has been used outside the U.S. for four decades to treat anxiety and depression. The clinical trials also provided "compelling" evidence that ONFI reduces the weekly rate of drop seizures in LGS patients.

Key safety issues related to somnolence/sedation and adverse events related to withdrawal. Both of these issues were addressed in the labeling for the drug.

Another important issue concerned the carcinogenicity and reproductive toxicity studies submitted with the NDA, which were conducted prior to 1978 and were deemed inadequate by current standards. The review team concluded that these inadequacies could be addressed with post- rather than pre-approval studies, based on several considerations: (1) the seriousness of the disease; (2) the limited treatment options approved for LGS, and the toxicities associated with them; (3) the extensive postmarketing experience for clobazam outside the United States; and (4) the availability of "some" data regarding these issues.

PICATO (ingenol mebutate)

There was no express risk-benefit assessment for this topical treatment for actinic keratosis. Statistically significant results were seen in four clinical trials, which assessed efficacy in two different areas of the body (face/scalp and trunk/extremities).

The most serious safety issues related to eye disorders associated with eye exposure, including severe eye pain, eyelid edema, eyelid ptosis, and periorbital edema. The approved labeling included warnings to emphasize the importance of hand washing and avoidance of accidental transfer of the drug to the eye.

STENDRA (avanafil)

There was no explicit risk-benefit assessment in the Office Director memorandum for this fifth-in-class, type 5 phospphodiesterase (PDE5) inhibitor treatment for erectile dysfunction (ED). The Deputy Office Director noted that efficacy was evaluated in 2

clinical trials, and significant benefit was seen in all age groups, degrees of severity of ED, and for all durations of ED. The overall safety profile was similar to that of other PDE5 inhibitors, warranting similar contraindication and caution language in labeling.

TUDORZA PRESSAIR (aclidinium bromide)

There was no explicit risk-benefit assessment in the Office Director memorandum. After discussing other currently available anticholinergics for COPD, the memorandum noted that "Aclidinium bromide demonstrated efficacy and the safety profile is consistent with other approved anticholinergic drugs in this class." The Office Director agreed with the review team that the NDA should be approved.

The memorandum focused on a demonstrated lung function improvement in patients with chronic obstructive pulmonary disease (COPD). The most serious potential risks were cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. These were a particular concern because the drug is an anticholinergic, and cardiovascular risks had been suggested but not ruled out for other COPD drugs in this class:

> [A]nticholinergic agents have well-recognized common side-effects, but there has been some added concern regarding possible cardiovascular (CV) effects based on a meta-analysis of 17 clinical trials in COPD. This concern was lessened in some part with the conclusion of the UPLIFT study which contradicted the findings of the meta-analysis and has given reassurance with Spiriva Handihaler [(tiotropium bromide)]. However, to confuse the issue further, an alternate tiotropium formulation delivered by the Respimat device, which is not approved in the US, has demonstrated numerical imbalances in all-cause mortality over placebo with no specific cause of death standing out. Presently, a large, prospective safety trial is underway to further evaluate potential CV risks with tiotropium Respimat.

The memorandum noted a "few" cardiovascular events in controlled trials for TUDORZA PRESSAIR, but also that "the database is small and the limited number of events prohibits any definitive conclusions." The memorandum concluded that the data were not compelling enough to require further study before approval, but a post-approval study should be performed.

XALKORI (crizotinib)

The risk-benefit assessment for this non-small cell lung cancer (NSCLC) treatment emphasized the high objective response rate (ORR) seen in two clinical trials, and a potential for the drug to be less toxic than conventional chemotherapy. Accelerated approval was granted, subject to verification of clinical benefit.

The drug was specifically approved for treatment of patients with locally advanced or metastatic NSCLC that is positive for anaplastic lymphoma kinase (ALK), as detected by an FDA-approved test. Compared to conventional chemotherapy, the drug was

associated with a marked elevation in response rate and duration of response in this patient population. The assessment noted that this would likely translate into an improvement in overall survival in the post-approval confirmatory trials.

Although the drug appeared to be less toxic than conventional chemotherapy, the Office Director memorandum noted an association with severe, life-threatening or fatal pneumonitis, with a frequency of 1.6% in clinical trials. The risk-benefit assessment noted that further follow-up and examination of the adverse event profile in a randomized trial was necessary to fully define the safety signals associated with the drug.

ZELBORAF (vemurafenib)

This drug was approved to treat advanced malignant melanoma, based on a randomized, active-controlled trial that demonstrated a significant improvement in overall survival. The risk-benefit assessment emphasized that only one other drug has demonstrated a survival improvement in this disease. The toxicity profile was also better than that of most cytotoxic chemotherapeutic agents, and was "clearly acceptable" for a disease that has a "dismal prognosis."

ZIOPTAN (tafluprost)

The first-cycle review resulted in a November 2011 Complete Response action letter for this ophthalmic prostaglandin analog used to reduce intraocular pressure in patients with open-angle glaucoma or ocular hypertension. The action letter primarily focused on product sterility issues.

The sponsor submitted a response to the action letter in January 2012, and the second-cycle review resulted in approval. There was no express risk-benefit assessment in the Office Director memorandum. The memorandum did note that the drug was not referred to an Advisory Committee because the drug is an of ophthalmic prostaglandin analog with similar potential risks and benefits as other members in this class, the benefits and risks of using prostaglandin analogs to treat elevated intraocular pressure have been previously discussed at an advisory committee meeting, the safety profile of tafluprost did not raise any new significant safety issues, the design of the clinical studies was similar to other approved drugs in this class, and there were no controversial issues that would benefit from further advisory committee discussion.