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FDA Approval of Obesity Drugs – A Difference in Risk-Benefit Perceptions

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Given the obesity epidemic, patients and physicians are clamoring for new treatments. Companies are responding with significant investment in drug development. Drugs provide an important therapeutic option when lifestyle modifications are insufficient for achieving weight loss goals and when surgery is not desired or warranted. However, in the last decade, three obesity drugs were removed from the U.S. market and until last month, only one new obesity drug has been approved since 1999. How is it possible to make sense of this curious duality of circumstances?

Perhaps developing drugs that satisfy efficacy and safety standards has proved too challenging. Dexfenfluramine and fenfluramine (the ‘fen’ in ‘fen-phen’) were removed from the U.S. market in 1997 following reports of valvular heart disease and pulmonary hypertension. Sibutramine was removed in 2010 because of increased risk of myocardial infarction and stroke. FDA reviewed three new drugs in 2010–2011, yet each was initially denied approval due to safety concerns. This year the FDA Advisory Committee (AC) reviewed proposed guidance requiring the assessment of cardiovascular risk for obesity drugs, thereby harmonizing requirements with those of diabetes drugs [1]. The AC voted 17-to-6 in favor of requiring manufacturers to rule out excess cardiovascular risk even when a theoretic risk or signal for cardiovascular harm was absent. To date, only the safety concerns around lorcaserin and phentermine/topiramate have been addressed sufficiently to garner FDA approval.

Some question whether new obesity drugs are being held to a higher regulatory standard. FDA’s mandate is to approve drugs when “benefits exceed risks”. Two cognitive factors may be affecting risk-benefit deliberations.

Tendency for dichotomous thinking

According to Berlin, “Organizing aspects of our realities into dichotomous ... categories is a pervasive, ordinary, and often useful habit of mind. However, when coupled with a search for certainty, this mode of understanding highlights

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extremes, superimposes a value hierarchy, [and] neglects nuances of meaning ...”
[2].

Dichotomous thinking is illustrated in FDA’s guidance for developing weight management products [3]. A drug is effective if there is a statistically significant decrease in body weight of 5% beyond the placebo effect or at least 35% of patients lose 5% of their body weight. Dichotomous efficacy endpoints are useful for sample size estimates and regulatory decision-making (a drug is either approvable or not). However, balancing benefits against risks requires that both be considered simultaneously, a more cognitively demanding task. Instead, AC members are asked whether a standard of benefit has been achieved and then whether an unarticulated (presumably individual) standard of safety is achieved, a dichotomous conclusion.

Differences in risk perception

According to Slovic, “Experts’ judgments appear to be prone to many of the same biases [in risk perception] as those of the general public, particularly when experts are forced to go beyond the limits of available data and rely on intuition” [4].

Long-term safety data on medications to manage weight have been unavailable at approval so AC deliberations reflect a diversity of perceptions. From a patient or clinical perspective, if the benefit is expected to outweigh the harm for one person randomly selected from a population then the benefit should outweigh the harm for N people randomly selected from that same population regardless of how large N is. From a societal or public health perspective, rare events can result in many patients with adverse outcomes if a drug is used broadly (as might be expected with an obesity drug). For instance, in the case of rofecoxib for arthritis, the absolute risk of myocardial infarctions was 1.8 per 1000 patient-years [5]; however, this translated to approximately 160,000 excess myocardial infarctions and strokes when projected to the number of patients who received the drug [6]. Such a number of adverse outcomes could erode public confidence in new drugs.

A proposal

It is difficult and inherently subjective to balance the apples of benefits against the oranges of risk. Three suggestions may help improve the transparency of risk-benefit deliberations for obesity drugs, as well as other drugs that are used broadly in the population and/or require Advisory Committee review.

First, FDA can encourage formal risk-benefit modeling to project the number of adverse health outcomes avoided through weight reduction against the number of serious adverse effects expected using a theoretical population of adults taking the drug.

Second, FDA can encourage more explicit discussion of patient and societal assumptions during AC deliberations. A substantial body of evidence suggests that cognitively priming individuals with reminders of their values is effective in encouraging them to behave in accordance with those values. The question “Do the available data demonstrate that the potential benefits of the drug outweigh the potential risks?” generally elicits a scientific rationale for an individual’s vote. A prompt could be added asking panelists to elaborate on the societal or patient perspective they used when weighing risks against benefits.

Third, value-based considerations can be made more objective and generalizable by assigning numerical values of risk-benefit perceptions from surveys of patients and physicians. To our knowledge, this type of analysis has not been presented to FDA for obesity drugs.

Those recommendations are consistent with the Institute of Medicine report on *Ethical and Scientific Issues in Studying the Safety of Approved Drugs* [7]. The committee defined a blue print for developing Benefit and Risk Assessment and Management Plans which includes a formal risk-benefit analysis incorporating stakeholder input and summarizing the scientific and ethical rationale for regulatory decisions.

Some Light at the End of the Tunnel?

In February, the AC again reviewed the obesity drug phentermine/topiramate and voted 20-to-2 in favor of approval. Qsymia (phentermine/topiramate) was approved July 17 as an addition to a reduced-calorie diet and exercise for chronic weight management [8]. In May, the AC reviewed lorcaserin again and voted 18-to-4 in favor of approval. Belviq (lorcaserin) received FDA approval July 26 [9]. What changed to make these drugs now seem better? Two aspects appear to be important in tipping the risk-benefit balance. First was societal pressure to address the obesity epidemic, i.e., the benefit perception of weight reduction increased. Second, more detailed postmarketing risk mitigation was offered by the companies during the AC review, i.e., risk perception improved with greater risk management. Qsymia was ultimately approved with a Risk Evaluation and Mitigation Strategy (REMS) consisting of a patient Medication Guide and elements to assure safe use (prescriber training and pharmacy certification). The primary goal is to mitigate concerns regarding birth defects with first trimester exposure to Qsymia. Qsymia will only be dispensed through specially certified pharmacies. Ten postmarketing commitments were required, including a long-term cardiovascular outcomes trial to assess the risk for major adverse cardiac events. Belviq was approved without a REMS, but six postmarketing studies were required, including a long-term cardiovascular outcomes trial.

Reviewing drugs is an inherently challenging task. Consideration of the cognitive factors influencing risk-benefit deliberations may be a useful step toward making the review of obesity drugs more transparent to physicians and patients. The tendency to think dichotomously inherently makes balancing the potential risks against the potential benefits of drugs difficult as does the inherent difficulty in adopting alternative perspectives (e.g., patient vs. society vs. regulator). Explicit discussions of this and reminders to advisory board members of their charge may help to overcome these challenges for the good of prospective patients.

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References

1. U.S. Department of Health and Human Services. [Accessed: June 19, 2012] Food and Drug Administration. "Briefing Information for the March 28–29, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee". <http://www.fda.gov/AdvisoryCommittees/>

[CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm297239.htm](#)

2. Berlin SB. Dichotomous and Complex Thinking. *Social Service Review*. 1990 Mar. Vol. 64(No. 1): 46–59.
3. U.S. Department of Health and Human Services. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Guidance for Industry: Developing Products for Weight Management (*Draft Guidance*). 2007 Feb.
4. Slovic P. *Science*. 1987 Perception of risk. Apr 17; 236(4799):280–285.
5. Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *The Lancet*. 2004; 364(9450):2021–2029.
6. Topol EJ. Failing the Public Health — Rofecoxib, Merck, and the FDA. *New England Journal of Medicine*. 2004; 351(17):1707–1709. [PubMed: 15470193]
7. Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs. *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*. Washington, DC: National Academies Press; 2012. <http://www.iom.edu/Reports/2012/Ethical-and-Scientific-Issues-in-Studying-the-Safety-of-Approved-Drugs.aspx>. Posted May 1, 2012. [Accessed May 25, 2012]
8. U.S. Food and Drug Administration. [Accessed July 18, 2012] FDA News Release: FDA approves weight management drug Qsymia. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312468.htm>.
9. U.S. Food and Drug Administration. [Accessed July 18, 2012] FDA News Release: FDA approves Belviq to treat some overweight or obese adults. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm309993.htm>