



A Heavy Burden: Rethinking the F.D.A.'s Safety Balancing in the Evaluation of Weight Loss Medications

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A Heavy Burden: Rethinking the F.D.A.'s Safety Balancing in the Evaluation of Weight Loss Medications

This paper is submitted in satisfaction of the Food and Drug Law Winter Term course requirement.

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Abstract:

The Food and Drug Administration has recently rejected three drugs for the treatment of obesity based on safety concerns, engendering debate about the standards the Agency should use in evaluating weight loss medications. The debate surrounding these pharmaceuticals is related to two features that make their benefit difficult to evaluate, the particular subjectivity of the benefits they provide and their third party effects. These features tend to exacerbate differences between FDA evaluation of benefit and the evaluation of third party stakeholders. Because the FDA's safety evaluation relies inherently on an evaluation of benefit, these differences may lead to very different analyses of a drug's safety. While a more quantitative evaluation of drug benefits may help to resolve some of the issues that arise from the subjectivity of the benefits associated with weight loss drugs, it will not be able to eliminate or accurately reflect individual differences. This kind of analysis may clarify FDA decision making and make risk-benefit profiles more concrete for patients, but to account more fully for the individuality of benefit associated with this class of pharmaceuticals, the FDA should use a more relaxed safety standard to allow for a broader range of treatment options for obese patients. In contrast to the subjectivity of their benefits, the third party effects of weight loss drugs should not be a factor in the FDA approval process; rather, these effects should be taken into account through other kinds of policymaking.

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Introduction

The Food, Drug, and Cosmetic Act (FDCA) requires manufacturers of new drugs to demonstrate the safety and efficacy of these products to the Food and Drug Administration (FDA) prior to marketing.¹ To make this demonstration, a manufacturer must present evidence showing that its drug produces a greater effect than does a placebo, and that the benefits its drug provides outweighs the drug's risks.² This latter demonstration of safety requires a challenging comparison of positive and negative drug effects that may not lend themselves easily to commensurable measures. The FDA has generally performed this comparison in a process that, while certainly data-driven, is relatively ad hoc.³

The difficulty associated with making such a risk-benefit comparison is especially pronounced in the case of drugs to treat conditions that include lifestyle components, like drugs designed to treat overweight and obese patients by helping to induce weight loss. While these drugs may provide health benefits comparable to drugs intended to treat more traditional categories of disease, they also provide more subjective benefits to elements of quality of life, like heightened self-esteem and

¹ 21 U.S.C. §355(d).

² Peter Barton Hutt, Richard A. Merrill, and Lewis A. Grossman, *Food and Drug Law*, 3rd Edition, New York: Foundation Press (2007), 685-693.

³ Hutt, 696. Institute of Medicine (U.S.), Committee on the Assessment of the US Drug Safety System, Alina Baci, Kathleen Stratton, Sheila P. Burke, Editors, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (2007). Douglas C. Throckmorton, *Risk and Benefit in the Drug Regulatory Setting*, CDER presentation, November 6, 2007, Available online at: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM203016.pdf>. Louis P. Garrison, Jr., Adrian Towse, and Brian W. Bresnahan, *Assessing a Structured, Quantitative Health Outcomes Approach to Drug Risk-Benefit Analysis*, 26 *Health Affairs* (2007) 684.

increased community interaction.⁴ These elements may well be important parts of patient health, but may also be difficult to measure and vary substantially between patients.

The recent spate of FDA rejections of manufacturer applications to market new weight loss drugs, and the disgruntled response from many in the obese and obesity treatment communities, indicates that there may be a misalignment between the way FDA evaluators compared to doctors and patients weight these more subjective benefits against acknowledged safety concerns.⁵ As American waistlines continue to expand and both the demand for effective obesity treatment and the diversity of affected patients grow with them, this misalignment may lead to increasing dissatisfaction with the FDA's decision-making process, among manufacturers, doctors, and patients.

Commentators, both internal and external to the FDA, have suggested that a more quantitative approach to assessing risks and benefits of drugs would make the approval process both more accurate and more transparent.⁶ Undoubtedly, a comparison based on QALYs or a similar measure would help to clarify the elements of risk and benefit the FDA considers and the way it weights these elements against one another. Such transparency would ease the work of drug manufacturers, who could

⁴ See Jennifer T. Fine, et al., *A Prospective Study of Weight Change and Health-Related Quality of Life in Women*, 282 JAMA (1999) 2136, noting that data on weight change and health-related quality of life are limited. See also Ford, E. S., Moriarty, D. G., Zack, M. M., Mokdad, A. H., Chapman, D. P. *Self-reported Body Mass Index and Health-related Quality of Life: Findings from the Behavioral Risk Factor Surveillance System*, 9 Obes Res. (2001) 21. Heo, M., Allison, D. B., Faith, M. S., Zhu, S., Fontaine, K. R. *Obesity and Quality of Life: Mediating Effects of Pain and Comorbidities*, 11 Obes Res. (2003) 209, documenting relationship between BMI and health-related quality of life, but not documenting effects on many social and psychological dimensions. See also Rebecca M. Puhl and Janet D. Latner, *Stigma, Obesity, and the Health of the Nation's Children*, 133 Psychological Bulletin (2007) 557, discussing psychological and social impact of weight stigma on children. Neal Krause and Estina Thompson, *Negative Interaction and Body Weight in Later Life*, 45 International J. of Aging and Human Dev. (1997) 305.

⁵ See Downey and Kushner quotes in Andrew Pollack, *F.D.A. Declines to Approve Diet Drug*, New York Times (February 1, 2011). See Lovejoy and Blackburn quotes in Rob Stein, *Weight Loss Drug Withdrawal Latest Blow to Obesity Fight*, Blue News, Blue Cross Blue Shield Association (October 9, 2010). See Blackburn quote in Scott Allen, *In Fat War, Doctors Have Few Weapons*, Boston Globe (April 1, 2004).

⁶ See footnote 3.

adapt their presentation of research findings to better serve the FDA's evaluative model and the work of FDA evaluators who would receive more usefully organized information and benefit from a clearer model for analyzing it. It would also help to legitimate the FDA's decisions to the public, who would be better able to understand the decision-making process; it would also allay concerns that different categories of drugs were treated unevenly.⁷

Nevertheless, adoption of a more quantitative model would import the model's shortcomings. Among the most widely used and endorsed metrics for comparing risks and benefits of health interventions is the QALY.⁸ While the QALY is a useful tool, a continuing challenge in its development is accurately capturing preferences in order to quantify the impact of different health states on quality of life.⁹ Health interventions that provide particularly subjective benefits, varying substantially in their quality of life effects across patients, will be especially hard to capture accurately using QALYs.

Quantification, then, may fail to address the particular difficulties in comparing the risks and benefits of weight loss drugs. Indeed, for these and other drugs with highly subjective benefits, the FDA may instead need to consider a greater role for doctors and patients in performing the necessary balancing. By relaxing the safety standards it applies, allowing drugs with a less appealing risk-benefit profile than those that currently make it through the process, the FDA could create space for patients to bring their individual characteristics and preferences to bear on decisions about weight loss treatment.

⁷ See Blackburn comments cited in footnote 3.

⁸ Peter J. Neumann and Dan Greenberg, *Is the United States Ready for QALYs?* 28 Health Aff. (September 2009).

⁹ See Erik Nord, Norman Daniels, and Mark Kamlet, *QALYs: Some Challenges*, 12 Value in Health, Issue Supplement (March/April 2009) s10.

The FDA should be careful, however, to clarify that any such revision of its current safety standards is meant to allow for such individual decision-making and not as a means to address social costs imposed by the obesity epidemic. While these costs are a relevant political concern, an attempt to integrate them into the drug approval process would change the nature of the information the FDA considers.¹⁰ The FDA's public health mission certainly encompasses measures meant to address the obesity epidemic, but these measures should not bear on the FDA's evaluation of drug safety. Rather, to retain the legitimacy of the drug approval process, the FDA must continue to focus it on health and quality of life effects of an intervention on treated patients.

Recent Rejections

In the past year, the FDA has accepted the recommendations of Advisory Committees to reject two drugs developed to treat obesity, Arena Pharmaceuticals Inc.'s locaserin and Vivus Inc.'s Qnexa, as well as withdrawing a previously approved obesity medication, Abbott Laboratories' Meridia, from the market. Most recently, the FDA rejected an Advisory Committee recommendation to approve the obesity drug Contrave, requiring its creator, Orexigen, to carry out a long-term double blind study to determine the risk of adverse cardiovascular events in patients treated with the drug in order to gain approval.¹¹

These events leave obese patients with limited treatment options. Only one pharmaceutical product, Roche's Xenical, is currently approved for treating obesity and

¹⁰ See Alicia Mundy, *Senator Slams F.D.A. Advisory Committee's Avastin Decision*, Wall Street J. Health Blog (July 29, 2010), available online at: <http://blogs.wsj.com/health/2010/07/29/senator-slams-fda-advisory-committees-avastin-decision/>.

¹¹ Gupta, Sanjay and Elizabeth Cohen, *FDA Rejects Another Obesity Drug*, The Chart, CNN Health (February 1, 2011), available online at: http://thechart.blogs.cnn.com/2011/02/01/fda-rejects-another-obesitydrug/?utm_source=feedburner&utm_medium=feed&utm_campaign=Feed%3A+rss%2F+Blog%3A+Paging+Dr.+Gupta&replytocom=142496.

it is associated with unpleasant side effects.¹² Diet and exercise, while clearly the least invasive option for achieving weight loss, is ineffective for many obese patients.¹³ And weight loss surgery, an increasingly popular option, carries risks of serious complications and death, and costs substantially more than pharmaceutical options.¹⁴

Meanwhile, thirty-four percent of Americans are obese and sixty-eight percent are overweight.¹⁵ In 2004, the FDA issued a report detailing its plans for addressing this epidemic. The report focused on the FDA's important goals in improving food labeling and increasing consumer education about nutrition. The report's treatment of therapeutics to treat obesity, however, was brief and supported but deferred reconsideration of the standards used to approve or disapprove weight loss drugs.¹⁶

Statutory Standards for Approval

The FDA has a statutory obligation to approve only those drugs that it deems both safe and efficacious for their promoted use.¹⁷ These standards, however, are broad, leaving the FDA with wide discretion to shape its criteria for drug review. The FDCA does not define safety, nor has the FDA laid out its criteria for safety in regulations.¹⁸ The FDCA does require that efficacy be proved by well-controlled studies, which the FDA has taken to mean randomized, well-controlled studies, typically more than one,

¹² Reuters, *Factbox: Timeline and Facts About Obesity Drugs* (September 15, 2010), available online at: <http://www.reuters.com/article/2010/09/15/us-obesity-drugs-factbox-idUSTRE68E68M20100915>.

¹³ David Joel Goldstein, *The Management of Eating Disorders and Obesity*, Second Edition, Humana Press (2005) 279.

¹⁴ *Pros and Cons of Weight Loss Surgery*, WebMD, available online at: <http://www.webmd.com/diet/guide/is-weight-loss-surgery-right-for-you>. Lesley Alderman, *After Weight Loss Surgery, the Costs Can Pile Up*, New York Times (December 31, 2010).

¹⁵ Belluck, Pam, *Obesity Rates Hit Plateau in U.S., Data Suggest*, New York Times (January 13, 2010), available online at: <http://www.nytimes.com/2010/01/14/health/14obese.html>.

¹⁶ Food and Drug Administration, *Calories Count: Report of the Working Group on Obesity* (March 12, 2004), available online at: <http://www.fda.gov/Food/LabelingNutrition/ReportsResearch/ucm081770.htm>.

¹⁷ 21 U.S.C. §355(d).

¹⁸ Hutt 685.

showing that the treatment performs significantly better than the control, from both a statistical and clinical perspective.¹⁹

These efficacy results are, in practice, intimately related to the FDA's safety evaluation, as the FDA accounts for benefit in its decision on safety.²⁰ Indeed, before the efficacy requirement was explicitly added to the FDA's review process, its safety analysis implicitly required an evaluation of efficacy.²¹ No drug is completely safe; any chemical compound meant to affect the body's structure or functioning is likely to carry risks and side effects in addition to its therapeutic effect.²² Necessarily, then, the requirement that a drug be safe requires a risk-benefit analysis. A safe drug is not a drug that involves no risk to patients, but rather a drug that involves risks outweighed by the therapeutic benefit it provides. An entirely ineffective drug could not be safe, since it would provide no benefit but necessarily involve some level of risk. As the efficacy of an evaluated drug increases, however, the level of tolerable risk also rises, so that for a drug that provides very important therapeutic benefits, substantial risk might be allowed without condemning the drug as unsafe.

Approval Standards for Weight Loss Drugs

The FDA has adopted clear benchmarks for the level of efficacy the manufacturer of a new weight loss drug must demonstrate to gain approval. An FDA guidance document explains that "in general, a product can be considered effective for weight management if, after one year of treatment" either one of two scenarios is true. First, there could be a difference of five percent in mean weight loss between treated and

¹⁹ Hutt 688-691.

²⁰ Hutt 685.

²¹ George Larrick, "Drug Safety" Testimony, Hearings Before a Subcommittee of the House committee on Government Operations, 88th Congress 2d Session (1964), in Hutt.

²² Bernadine Healy, *What is a "Safe" Drug* U.S. News & World Report (December 13, 2004) at 37, in Hutt.

placebo groups that is statistically significant. Second, the proportion of patients who lose five percent or more of their body weight in the treated group could be at least 35% and approximately double the proportion in the placebo group, and statistically significant. The Agency will also factor in changes in obesity-related comorbidities.²³

The standards for evaluating the safety of weight loss products, however, are less clear cut. The FDA's guidance to industry suggests some factors to monitor, including cardiac valvulopathy and potential for abuse, which have been problems for weight loss products in the past.²⁴ Other than this brief guidance, however, safety evaluation of weight loss drugs is left to the standard ad hoc comparison of drug risks and benefits.

The way that the FDA evaluates the benefit associated with weight loss, therefore, is left open; its statutory obligation to approve only safe and effective drugs gives a broad enough definition of safety to leave both of these elements largely to the agency's interpretation. One commentator has argued that "no one has yet defined safety and efficacy."²⁵ Certainly, both statutes and regulation leave the agency discretion to reconsider the way it balances risks and benefits for a particular category of drugs.

The agency has the authority, therefore, to reconsider the way that it evaluates the safety of weight loss drugs. I argue that it should reconsider the way it considers the benefits associated with weight loss, because these benefits are so highly subjective. On the other hand, I argue that it should not take social or economic costs into account,

²³ Food and Drug Administration, *Guidance for Industry: Developing Products for Weight Management* (February 2007), available online at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf>.

²⁴ *Ibid.*

²⁵ Joseph Cooper, *Purpose, Technique and Strategy in the Regulation of New Drugs*, in Richard Landau, ed, *Regulating New Drugs*, Chicago: University of Chicago Press (1973) 30.

although they should play a part in shaping other aspects of policy affecting obesity treatments.

Difficulties with Evaluating the Benefit of Weight Loss

The evaluation of drug safety requires not only a determination of whether a drug is effective in achieving the result it promises, but also an evaluation of the importance of the result. The tolerable level of risk for a drug effective in curing an otherwise terminal illness will be higher than the tolerable level of risk for a drug effective in treating an irritating, but not life-threatening, condition. For instance, a drug that could cure cancer but caused severe nausea would almost certainly be approved as safe. A drug that threatened the same side effect, but was very effective in treating dandruff, would probably not pass FDA muster. In this extreme example, the relative importance of the therapeutic benefits is easy to evaluate. In many cases, however, evaluating the importance of the effect a drug achieves is more difficult and therefore determining what level of risk is acceptable is not straightforward.

The importance of a benefit like weight loss is challenging to evaluate for at least two reasons. First, the value of the benefit is more subjective than that of a life-saving treatment, or even of a treatment that ameliorates a more universally painful or irritating condition. While there are certainly variations in the extent to which people dislike things like aches, pains, and dandruff, and even variation in the valuation of life from person to person, almost everyone ranks pain and loss of life as bad and almost everyone can agree that less pain is always better than more.

There is, in contrast, substantial disagreement across cultures and across persons about what weight is ideal, making it difficult to pinpoint the level of body mass at which weight loss drugs would produce a valuable as opposed to a detrimental effect.²⁶ Whether obesity should even be characterized as a disease is open to debate.²⁷ And though the health effects associated with obesity are clearly bad, the occurrence of these effects varies among groups and persons.²⁸

To the extent that obesity is bad because it bears a causal relationship to conditions like diabetes, stroke and heart attack, it differs importantly from conditions that are bad in themselves. If a treatment can ameliorate a condition that is bad in itself, it creates a certain benefit in patients. In contrast, a weight loss drug might decrease BMI without affecting the likelihood of the occurrence of negative health events in any particular treated patient, or, in fact, in most treated patients; since the efficacy of weight loss drugs is demonstrated via intermediate endpoints, their effect on adverse health events is far from clear. Unlike a drug that treats a condition that no one or almost no one would want to have, weight loss drugs have an effect that may be more

²⁶ See Rashida R. Dorsey, Mark S. Eberhardt, and Cynthia L. Ogden, *Racial/Ethnic Differences in Weight Perception*, 17 *Obesity* (2009) 790, describing racial and gender differences in accuracy of perception about being over and under-weight. See also Michele L. Ver Ploeg, Hung-Hao Chang, and Biing-Hwan Lin, *Over, Under, or About Right: Misperceptions of Body Weight Among Food Stamp Participants*, 16 *Obesity* (2008) 2120, describing differential misperception of weight status depending on several socioeconomic variables.

²⁷ See Allen Steadham, *Obesity is Not a Disease*, 1 DocNews, American Diabetes Association (October 2004), available online at: <http://docnews.diabetesjournals.org/content/1/2/10.1.full>. See also Laura Johannes and Steve Stecklow, *Dire Warnings About Obesity Rest on Slippery Statistic*, Wall Street J. (February 9, 1998).

²⁸ See Centers for Disease Control, *About Adult BMI*, updated February 15, 2011, available online at: http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html. See also Minet Kinge J, Morris S. *Socioeconomic variation in the impact of obesity on health-related quality of life*, 71 *Soc. Sci. Med.* (November 2010) 1864, noting variation on effect of obesity on health-related quality of life by SES. See also Serena Low, Mien Chew Chin, Stefan Ma, Derrick Heng, Mabel Deurenberg-Yap, *Rationale for Redefining Obesity in Asians*, 38 *Ann. Acad. Med. Singapore* (2009) 66, describing different relationship between BMI and risk factors for Asians than for other ethnicities, as well as between Asian ethnic groups. See also Stacy A. Ogbeide, Christopher A. Neumann, Brian A. Sandoval, and C. Diane Rudebock, *Gender Differences Between Body Weight and Psychological Well-Being During Young Adulthood: A Brief Report*, 8 *The New Psych. Bulletin* (2010) 41, reporting differential effects by gender of BMI on well-being.

or less desirable to different people depending on their desired weight, other values, and the impact of a lower BMI on their particular health status.

Second, obesity has an apparent public health impact that extends beyond its effect on individual patients. The obesity epidemic has made headlines and garnered political attention not only because American weight gain burdens heavy individuals, but because it has at least arguably placed a substantial burden on society. Obese persons are more prone, on average, to the chronic diseases that drain health care resources, requiring Americans to pay more to support their care, both through taxes and health insurance premiums.²⁹

Finding an effective, non-invasive treatment for obesity could help to ameliorate this financial burden. The FDA, however, has steadfastly ignored the kind of cost-benefit analysis that would take these societal effects of a treatment under review into account, focusing instead only on the risks and benefits of a drug to treated patients.³⁰ It might be argued, however, that the expense of obesity-related health complications combined with the more general crisis in health care spending might press for a more comprehensive consideration of treatments like weight loss drugs, for which these wider societal effects may be substantial.³¹

Some have argued that the FDA holds weight loss drugs to a higher standard of approval than other treatments.³² It is impossible to know whether this claim is true, but given the issues discussed above, it is understandable that the FDA has approved fewer

²⁹ See Wolf AM, Colditz GA. *Current estimates of the economic cost of obesity in the United States*, 6 *Obes. Res.* (March 1998) 97, for one estimate of the economic cost of obesity.

³⁰ Dale H. Gieringer, *The Safety and Efficacy of New Drug Approval*, 5 *Cato Journal* (Spring/Summer 1985) 182.

³¹ See, e.g., Morgan Downey, *FDA Goes AWOL on Obesity*, Downey Report (October 29, 2010), available online: <http://www.downeyobesityreport.com/tag/vivus-pharmaceuticals/>.

³² See footnote 5.

weight loss drugs than some commentators think is optimal. The health and quality of life detriment associated with obesity is not well-defined and may be very subjective, making the benefit of ameliorating obesity difficult to evaluate. Moreover, to the extent that commentators who favor less stringent standards for the review of weight loss drugs are, in part, driven by a concern about the social and economic impact of obesity, their evaluation of treatments is very likely to come out more often in favor of approval than the FDA's, as they are excluding these factors from consideration.

Contrave

The FDA's refusal to approve immediate marketing of Contrave this February illustrates this difficulty. There was no question that Contrave met one of the FDA's benchmarks for efficacy of a weight loss drug, as the proportion of treated patients losing 5% or more of their body weight was double that proportion in the placebo group.³³ An Advisory Panel recommended approval of the drug, based in part on this efficacy finding.³⁴

Nevertheless, the FDA rejected this recommendation and demanded an additional large, long-term clinical trial on the basis of safety concerns. Because the completed trials showed a small increase in blood pressure and pulse rate associated with Contrave use, the FDA wanted to determine whether the drug was associated with an elevated risk of side effects like heart attack and stroke over the longer term.³⁵ Clearly, the FDA was engaging in a risk-benefit analysis for treated patients; its demand

³³ Pollack (2011).

³⁴ Andrew Pollack, *F.D.A. Panel Backs Drug to Treat Obesity*, New York Times (December 8, 2010), available online at: <http://query.nytimes.com/gst/fullpage.html?res=9B05E4DE1231F93BA35751C1A9669D8B63&>.

³⁵ Pollack (2011).

for additional studies reflected a concern that the risk, even if small, of serious negative side effects of Contrave outweighed the weight loss benefit it provided.

It is equally clear that commentators disappointed by FDA's failure to approve Contrave could have come to a different conclusion about its safety. First, they might have weighted the benefit associated with Contrave's effect on weight loss more heavily than did the FDA. If they believe that the health and quality of life impact of even a modest decrease in BMI is substantial, they might see it as significant enough to outweigh the risks associated with the small blood pressure and pulse rate increases in the Contrave-treated patients. Further, if they included in Contrave's benefits the social and economic impact of providing a non-invasive obesity treatment that is more effective than diet and exercise alone, a comparison of its benefits and risks would be even more likely to come out in its favor.

Amending Safety Criteria

Critics both internal and external to the FDA have pushed for greater clarity and transparency in the FDA's process of weighing risks and benefits. Currently, the process is fairly ad hoc, with regulators holistically evaluating evidence of risks and benefits, then rendering a decision as to whether on balance the drug's positive effects outweigh its potential negative impact. These critics have suggested that a more quantitative process might help to mitigate this lack of transparency; by identifying ways of quantifying risks and benefits, their comparison can be more effectively articulated.³⁶

³⁶ See footnote 3.

Indeed, the standards the FDA has used to evaluate weight loss drugs are not clear. The agency generally does not comment on the reasons for its drug approval decisions, so that the means by which it weighs risks and benefits have not been spelled out.³⁷ In the case of Contrave, the FDA's demand for additional studies was clearly based on its concern about increased blood pressure and pulse rates in the treatment group. It was not clear, however, how the FDA weighed this potential risk against the benefits obese patients would forgo as a result of keeping the drug off the market longer. Indeed, the fact that the Advisory Committee and the Agency came to different decisions implies that the risk-benefit comparison did not yield an obvious conclusion.

Some commentators have suggested the use of QALYs to capture risk and benefit in the drug evaluation process.³⁸ Using a QALY-based metric to evaluate safety does offer several important advantages over the current system of evaluation generally. First QALYs offer a way to compare risks and benefits that might otherwise be incommensurable. While effectiveness measures a claim about a drug's effect on a particular condition, and can therefore generally be captured by measuring changes in disease-specific measures, the safety evaluation requires weighing these benefits against a range of side effects. While curing a disease is clearly good and suffering from a rash, nausea, or dry mouth is clearly bad, it is difficult to know exactly how to weigh these outcomes against one another absent a common metric. QALYs provide such a metric and in so doing give evaluators an objective and consistent means of evaluating drugs.

Using a QALY-based metric would also avoid some of the current issues with using intermediate endpoints to evaluate drugs. Since all of the health-related outcomes

³⁷ Pollack (2011).

³⁸ See Louis P. Garrison, Jr., Adrian Towse, and Brian W. Bresnahan, *Assessing a Structured, Quantitative Health Outcomes Approach to Drug Risk-Benefit Analysis*, 26 Health Affairs (2007) 684.

associated with a particular treatment would be translated into QALYs, there would be less need to extrapolate from intermediate effects to longer term outcomes. In the case of weight loss medications, the use of QALYs might more effectively capture for immediate benefits in functionality and attitude associated with even moderate weight loss, without needing to demonstrate longer term effects on morbidity and mortality (although these effects, to the extent that they could be determined, would certainly still be relevant to the QALY analysis).

While quantification would help to make the FDA's process more transparent and comprehensible, use of QALYs or similar measures would import many of the problems associated with these measures. These problems are pronounced in the context of weight loss drugs because their effect on individual quality of life may differ so substantially from individual to individual. An important problem with the development of QALY metrics has been the measurement of preferences for different health states. Different methods for measuring preferences have led to different results, making it difficult to accurately reflect the impact of being in a particular health state on quality of life.³⁹ Preferences for weight loss are likely to differ even more than preferences for interventions that decrease pain or correct clear disability. While QALY analysis may help to illuminate the risks-benefit profile associated with a particular drug on average, they are unlikely to accurately reflect the risk-benefit judgment that any particular fully informed individual might reach.⁴⁰

³⁹ Nord. See also Garrison.

⁴⁰ QALYs also make an assumption of risk neutrality that may not hold true for many individual patients. Newer techniques, however, offer the possibility of analysis that does not assume particular risk preferences. See F. Reed Johnson, *Between Regulatory Rocks and Hard Places: Quantifying Tolerance for Pharmaceutical Risks*, ISPOR Connections (May 6, 2008), available online at: <http://www.ispor.org/news/articles/Dec08/BRRHPQTPR.asp>.

QALY analysis may be helpful, however, in helping to express risks and benefits effectively to patients. The concept of a quality adjusted life year is relatively intuitive and knowing the average QALYs associated with a drug could help to inform patient decision making, particularly in conjunction with a provider that can help to explain the factors included in the QALY analysis and the ways in which that analysis might and might not reflect that patient's particular situation. Especially if a patient finds very small risks insufficiently concrete to weigh accurately, QALY analysis might help to put those risks in clearer terms. This use of QALY analysis fits well with the mandate in the 2007 Food and Drug Amendments for the F.D.A. to communicate better with patients about the risks and benefits of new drugs, by offering the F.D.A. another tool, potentially more cognizable for patients, to express information about risk-benefit profiles.

Relaxed Standards for Weight Loss Drugs

Weight loss drugs, more so than most other therapeutics, confer benefits that may be valued very differently between patients. The FDA is, therefore, in a poor position to weigh the risks and benefits of these pharmaceuticals accurately for patients as a whole. This difficulty should imply a less stringent safety standard than the FDA currently seems to require for obesity drugs. Using a less stringent safety standard would allow individual patients, in consultation with their physicians, to make their own risk-benefit calculations. For a patient whose lifestyle is substantially impaired by his obesity, accepting some increased risk of cardiovascular events might be reasonable.

For another patient, obesity might create health risks but might not involve any major lifestyle impairment. For this patient, the same set of side effects might make the drug a poor choice, if those side effects are not outweighed by the health benefit associated with the drug's promised weight reduction.

Relaxed safety standards would have the additional advantage of allowing physicians to make more individualized determinations about the appropriateness of therapeutics for patients with different BMIs. Health risks associated with an elevated BMI may vary across patients with different characteristics.⁴¹ If the FDA applies very stringent safety standards to weight loss drugs, these drugs may not be available to even those patients who are most at risk. A more relaxed standard would allow physicians to evaluate risks and benefits of the drugs for individual patients so that patients at substantial risk could receive treatment, even at the expense of some side effects that would not be tolerable for patients at less risk.⁴²

Allowing for this patient specific determination falls within the FDA's core mission of protecting public health. Acknowledging the subjectivity inherent in evaluating the health and quality of life benefits associated with weight loss does not demean the importance of the health of obese patients. Instead, it puts them in better control of their health, allowing them to consider the impact of treatment versus non-treatment on their health and well-being. By offering an alternative treatment for some

⁴¹ See footnote 28.

⁴² Because Contrave is a combination of two drugs approved separately by the FDA for other uses, it is conceivable that a physician who believed it would provide an important benefit for an obese patient could cobble these available therapies together off-label. This solution, however, is likely to be help only a limited number of patients, since the manufacturers of the available therapies could not promote their use in obesity treatment, limiting the dissemination of knowledge about that use. Additionally, a new drug developed for obesity that was not a combination of currently approved therapies would be set entirely off limits to obese patients should the FDA refuse to approve its use, so that the off-label possibility for Contrave does not solve the larger policy problem created by limited access to potentially effective obesity medications.

patients who might otherwise lack viable treatment options, relaxed approval standards for weight loss drugs could promote the effective treatment of obesity and therefore improve the public health. Consideration of the limited alternative treatments available for obesity and the importance to the public health of offering patients a reasonable range of treatment options is in line with the factors the Agency generally considers in making approval decisions.⁴³

Almost certainly, some patients, even in consultation with their doctors, will make risk-benefit decisions that fail to promote their health, leaving them less healthy by virtue of the drug's approval than they would have been otherwise. Protecting patients from the possibility of this kind of error is part of the purpose of requiring F.D.A. approval for new drugs; by not allowing drugs with risk-benefit profiles below a certain level, the F.D.A. promotes the public health by keeping off the market products that would present a risk of this kind of mistake for substantial numbers of patients. Certainly the approval process for weight loss drugs should not be eliminated altogether. A drug that was totally ineffective presents a situation in which no patient could make a reasonable risk-benefit decision to be treated; ineffective drugs, then, should continue to be kept off the market. Drugs that present severe and certain safety risks might present a similar situation. If the risks associated with a drug are such that a reasonable patient certainly or almost certainly would not choose to be treated, the F.D.A. should not allow the drug to be marketed because almost any decision to be treated would demonstrate a mistake in risk-benefit analysis.

⁴³ For instance, in considering whether to expedite review of certain drugs, accelerate approval, or grant fast track or priority review status, the Agency considers the availability of other therapies. Food and Drug Administration, *Guidance for Industry: Available Therapy* (July 2004), available online at: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126586.htm>.

In many intermediate cases, however, patients will be better positioned than their physicians to make accurate risk-benefit tradeoffs, based on the particular benefits they associate with moderate weight loss. These more accurate judgments will result in a health-maximizing allocation of treatment, since the most accurate evaluation of risks and benefits, will lead to treatment decisions that tend to maximize total health benefits. This maximization argument is particularly true assuming a broad definition of health to include social and psychological components associated with weight loss. These elements of health are more difficult to evaluate, but remain important to individual health and therefore to the public health. By allowing patients, the parties most likely to understand and accurately predict these benefits to them, to make treatment decisions in a wider range of cases, these components of health will be more fully realized. Given the public health focus of the agency, its attention should be to this broader understanding of health.⁴⁴

Weight loss drugs also raise questions about the appropriate comparison group to be used in evaluating drug safety. To determine efficacy, the FDA typically compares treated patients to untreated patients, rather than patients who are treated with an alternative therapy. The standard for comparison of safety data, however, is less well articulated. Safety requires that a drug's benefits outweigh its risks, but neither risk nor benefit can be understood in a vacuum. In the case of weight loss drugs, risk and benefit must be evaluated in terms of the relevant alternatives for obese patients, which may vary importantly from patient to patient.

⁴⁴ See, e.g., Lawrence O. Gostin, *A Theory and Definition of Public Health Law*, Public Health Law: Power, Duty, and Restraint, Second Edition, University of California Press/Milbank Memorial Fund (2008).

Often, these alternatives are limited. Patients who continue to be obese risk serious long-term consequences for health and quality of life. Diet and exercise, while associated with few side effects, proves ineffective for many patients. Only one weight loss drug is currently on the market and it is associated with unpleasant side effects that may make long term use unrealistic for many patients. The only other therapeutic option is weight loss surgery, which carries its own serious risks. While evidence of increased blood pressure in the treatment group is a concern, the FDA should evaluate this concern against this backdrop of limited alternatives for obese patients.

Given these choices, it is plausible to think that some patients would prefer to incur the long-term potential risk of a cardiac event to avoid a surgery that poses at least some risk of death or even to an alternative drug that causes very unpleasant side effects that might substantially and immediately reduce quality of life. The pros and cons of the different treatment options, however, are problematically incommensurable absent in depth knowledge of a particular patient's preferences. Whether an uncertain risk of a cardiac event, a small but immediate risk of very serious consequences associated with surgery, or consistent long-term indigestion associated with an alternative drug are more or less preferable is not obvious or constant across persons; reasonable people could disagree about which side effects they would prefer to incur, or whether they want to risk side effects at all. Putting more choices in the hands of patients will allow expression of these individual preferences.

History and Reluctance – Steps Forward

It is possible that the FDA's recent decisions on weight loss drugs are also bound up with the history of diet pills and the reputational damage the Agency has suffered

from approval of drugs like “fen-phen” and, more recently, Meridia, that have turned out to have significant negative side effects.⁴⁵ Prior to the current regulatory regime, several weight loss drugs were marketed with tragic results.⁴⁶ But even since the inception of the modern regime, all but one of the drugs the FDA has approved for long-term use have been removed from the market because of safety concerns.⁴⁷ Both because of the popularity of these drugs in a society that glorifies thinness (even as it eats its way into obesity) and because of the perception that the benefits of these drugs are largely cosmetic and therefore frivolous, these negative side effects have been portrayed harshly by the media and treated by many as failures of FDA regulation.⁴⁸

Another debacle, however, is not a necessary or perhaps even probable result of the approval of a new weight loss drug. First, the social perception of obesity has continued to shift toward acceptance of obesity as a disease, such that its treatment is understood as more medical and less purely cosmetic.⁴⁹ Because of this increased recognition of the urgency of treating obesity, approval of a drug bearing some risks might be more easily accepted than it would have been in the past.

Further, the FDA has an opportunity to articulate the risk-benefit comparison it is making more clearly to the public and to place responsibility for assuming risk more

⁴⁵ Reuters, Steven Reinberg, *Weight-Loss Drug Meridia Pulled From U.S. Market*, Business Week (October 8, 2010), available online at: <http://prescriptions.blogs.nytimes.com/2011/03/28/this-weeks-health-industry-news-34/>.

⁴⁶ Thyroid extract, used in the 1800s, resulted in hyperthyroidism. Dinitrophenol was used in the 1930s, but led to nerve malfunction. See Reuters.

⁴⁷ Reuters.

⁴⁸ See Kate Cohen, *Dangerous Prescription: Fen Phen Nation*, Frontline (November 13, 2003), available online at: <http://www.pbs.org/wgbh/pages/frontline/shows/prescription/hazard/fenphen.html>.

⁴⁹ W.P.T. James, W.H.O. *Recognition of the Global Obesity Epidemic*, 32 International J. of Obesity (2008) S120. Judith Stern and Alexandra Kazaks, *Chronology, Obesity: a Reference Handbook*, Santa Barbara: ABC-CLIO (2009) 125-39. See also C.H.O.I.C.E. *campaign launched by makers of Lap-Band*, Health News Digest (May 25, 2010), available online at: http://healthnewsdigest.com/news/obesity%20issues0/Adult_Obesity_Need_for_Both_Prevention_and_Treatment_printer.shtml.

squarely in the hands of individual patients and physicians. If the FDA can communicate to the public that its rationale is grounded in its concern about the subjectivity of the benefits associated with weight loss and its concern to protect a wider sphere of patient and physician choice, it is likely to find a reasonably welcoming public reception.⁵⁰ A more tempered public reaction will be particularly likely if the FDA is able to communicate its risk concerns clearly, allowing potential patients to make truly informed decisions. QALY analysis may help in tackling this key challenge.

Social and Economic Effects – a Policy Problem for Another Agency

Obesity imposes costs on society apart from its health effects on individual patients. Care for chronic health problems associated with obesity is generally not paid for entirely out of pocket by individual patients. Rather, the costs of care are usually subsidized either by private insurance or by the public treasury in the form of Medicaid, Medicare, or other government-funded programs. In either case, people besides individual obese patients are bearing part of the economic cost associated with obesity. In the case of private insurance, other individuals in the insurance pool will pay higher premiums to cover the cost of care for obese patients.⁵¹ For government programs, taxpayers bear the cost of increased care usage for obese patients.

⁵⁰ See Maureen Cavanaugh, *Should Patients Have a Voice in FDA Drug Approvals?*, interview with Michael Calichman and Duane Roth, These Days, KBPS (January 31, 2011), available online at: <http://www.kpbs.org/news/2011/jan/31/should-patients-have-voice-fda-drug-approvals/>, including comments from speakers and public endorsing more patient involvement and choice. See also George J. Annas, *Cancer and the Constitution – Choice at Life's End*, 408 New Eng. J. of Medicine (2007). See also Nicholas J. Plionis, *The Right to Access Experimental Drugs: Why the FDA Should Not Deprive the Terminally Ill of a Chance to Live*, 16 William and Mary Bill of Rights J. (2008) 901.

⁵¹ This cost-shifting is especially true under PPACA, which mandates community rating, allowing premium differences based only on age, marital status, and whether one is a smoker. Under the pre-PPACA regime, obese patients might have been charged a higher premium in anticipation of their higher care consumption, so that the costs of obesity-related care did not fall on other members of the insurance pool.

Because individual patients do not bear the full cost associated with obesity, they may not make efficient decisions about treatment. An individual might forgo treatment because of an unpleasant side effect or the remote possibility of a very serious side effect, although treatment might have been the optimal choice from a social perspective, because these costs are outweighed by the social costs posed by continuing obesity and its associated health risks.⁵²

Similarly, the FDA, in analyzing risks and benefits to treated patients, as opposed to costs and benefits to society as a whole, may fail to approve treatments, although approval would be socially optimal. A drug could carry risks that outweigh the treatment benefit to the individual patient, but which are less than the benefit to society as a whole when relevant cost savings are taken into account. While the socially optimal outcome would be to approve the drug, the FDA's current methodology would reject it.

The external consequences associated with obesity are important and should play a role in shaping health policy. They are not, however, consequences that are best dealt with by the FDA for two reasons. First, the problem could not be easily addressed through the approval process alone. Second, it would interfere with the Agency's perceived legitimacy and conflict with its image as a public health authority.

While a lower safety standard could help to deal with the subjective preferences problem, it would not help to address externalities. It would allow subjective preferences to enter the decision-making process by making more options available to patients and doctors and allowing them to balance risks and benefits based on their

⁵² There is evidence that people tend to overweight very serious negative outcomes that are very unlikely to occur. See Charles F. Mason, Jason F. Shogren, Chad Settle, and John A. List, *Environmental Catastrophes and Non-Expected Utility Maximization: An Experimental Evaluation* (September 13, 2000), available online at: <http://uwacadweb.uwyo.edu/mason/working.papers/ecneumee.pdf>. See also Jason F. Shogren and Laura O. Taylor, *On Behavioral-Environmental Economics*, 2 Rev. of Env. Econ. and Pol. 26 (2008).

particular situations. Third party interests, however, would still be excluded from the decision-making process, as patients would not include social costs in their calculus. Because the approval process can only make more treatment options available, and cannot force patients to make socially optimal choices, changing it will be inadequate to address externalities resulting from under consumption of treatments.

Policy-making outside the FDA, however, can be brought to bear on these externalities. Payment policy, for instance, implemented through an agency like the Centers for Medicare and Medicaid Services (CMS) could help to address consumption. By lowering the cost to the patient of a socially desirable treatment, or by increasing the cost to the patient of care associated with forgoing treatment, government programs like Medicare and Medicaid could induce patients to engage in more socially optimal behavior. As private insurers often take cues in payment policy from public programs, payment changes in Medicare and Medicaid could have a broad impact on the choices that obese patients make.

Addressing social costs through payment policy has the additional benefit of keeping the FDA out of the realm of economic decision-making. While the decisions made currently by the FDA undeniably have wide-ranging economic impacts, the agency has been insulated from relying on economic rationales. The importance of this insulation is apparent from the negative public reaction to “death panels,” and to health care rationing generally.⁵³ Economics is a controversial ground for health care decision making, such that grounding lower safety standards for weight loss drugs in social cost

⁵³ Neumann and Greenberg. *See also* S.R. Tunis, *Why Medicare Has Not Established Criteria for Coverage Decisions*, 350 New Eng. J. of Medicine 2196 (2004).

concerns, rather than in an interest in protecting individual decision-making, risks severe political consequences for the FDA.

Indeed, this type of rationale is likely to garner controversy as grounds for payment decisions, as well. But CMS, as an agency responsible for paying for the health care patients will ultimately consume, may be more legitimately able to assert such a ground. Because of its payer role, CMS also occupies a different place than the FDA in the public consciousness. The FDA is generally among the most respected of the federal agencies, in part because it is understood to have a unilateral mission to protect the public health.⁵⁴ Despite blows to the FDA's reputation associated with approvals of drugs that have subsequently proved to have previously unrecognized adverse health consequences, as well as perceptions that the agency developed a more politically motivated slant during the Bush administration, the agency enjoys substantial public support.⁵⁵ In resting approval decisions solely on the health risks and benefits involved, the FDA stays true to its public health mission. While it is true that economic savings could be used to increase the public health in other ways, so that considering economic consequences of approval decisions is not necessarily out of line with the FDA's public health mission, this reasoning could bring such a wide range of factors within the FDA's decision-making purview that its role and purposes could become unacceptably blurred.

⁵⁴ See Michael R. Taylor, *Protecting the F.D.A.'s Ability to Protect the Public Health*, 61 Food & Drug L.J. 805 (2006).

⁵⁵ See James T. O'Reilly, *Losing Deference in the F.D.A.'s Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 Cornell L. Rev. 939 (July 2008). See also Lydia Saad, *CDC Tops Agency Rankings; Federal Reserve Board Lowest*, Gallup (July 27, 2009), available online at: <http://www.gallup.com/poll/121886/CDC-Tops-Agency-Ratings-Federal-Reserve-Board-Lowest.aspx#1>.

In also including economic considerations, the FDA would risk the legitimacy it enjoys in making drug approval decisions at all. By preventing patients from accessing some drugs, while allowing access to others, the FDA is limiting patient autonomy. To justify that limitation, the agency must play the role that gives the public reason to accept it. If the FDA were to accept less safety for more dollars saved, it would open itself up to criticisms that payment agencies and private insurers already face, that patient well-being is being sacrificed to fiscal constraints. These criticisms currently leave decisions by CMS and private insurers open to much greater scrutiny than FDA decisions.⁵⁶ To open FDA approval decisions to this kind of scrutiny could dampen its ability to expeditiously make the decisions and enforce them without substantial interference from courts or substantial objection from regulated parties.

Conclusion

In the face of what both the United States Department of Health and Human Services and the World Health Organization have described as an obesity epidemic, the FDA's recent rejection of three drugs intended to treat obesity, as well as its withdrawal of Meridia from the market, have left obese patients with relatively limited treatment options. While the FDA has cited safety concerns as the driving force behind all these decisions, commentators have suggested that the FDA's standards for evaluating weight loss drugs are unreasonably high. This mismatch between the FDA's evaluation and that of outside observers could relate to disparate understandings of the benefits that these drugs offered. These differing understandings probably result in part from

⁵⁶ Compare, for example, the current uproar over CMS approval of Provenge, to its relatively uncontentious FDA approval.

two characteristics of weight loss drugs, the subjectivity inherent in evaluating their benefits to patients, and the social benefits they may also offer.

The subjectivity of benefits could be addressed by relaxing the Agency's current standards for approval to give patients more leeway to weigh the risks and benefits of treatment for themselves. Given the particularly subjective nature of benefits associated with weight loss, such relaxation might be an appropriate response to critics of the Agency's recent rejections. In contrast, potential social benefits of weight loss drugs, while relevant to other health policy decisions, should not be considered as a part of the F.D.A.'s approval process, as their inclusion would both be both inadequate to ensure their consideration and would erode the Agency's legitimacy.

This analysis should also imply questions about the Agency's evaluation of other categories of drugs. Generally, a clearer formula for evaluating the safety of new drugs could help to enhance the legitimacy of FDA approval decisions. Specifically, the Agency should be aware of the subjectivity of the benefits of many drugs that may not be captured either in its current ad hoc process or in more quantitative approaches. Where these benefits are present, the Agency should incline more toward relaxation of safety standards than it would otherwise, allowing patients a greater scope of treatment autonomy. Identifying and evaluating such benefits will, however, pose a challenge, and could push toward greater patient involvement in the drug approval process.

Finally, however, the Agency should continue to exclude social cost concerns from its analysis. As the current debate over Avastin implies, the FDA will continue to face pressure over the role cost places in its decision making and it should continue to firmly exclude it. In being as clear as possible about its exclusion of cost considerations,

the FDA may also clear a path for CMS to give more credence to these considerations. Such clarity will help to define a division of labor between the two organizations, so that FDA approval need not be so close to a guarantee of CMS coverage.