

The Food and Drug Administration and the Future of Drug Development for the Treatment of Diabetes

Eric P. Brass, MD, PhD

The U.S. Food and Drug Administration (FDA) regulates the marketing of drugs in the United States. The FDA staff faces substantial challenges in evaluating preclinical and clinical trial data for a proposed new drug and deciding whether the resultant benefit-risk assessment supports marketing approval. Any approval decision will be associated with uncertainty regarding the drug's true risks and benefits because of the inherent limits of testing in pre-approval development programs, the sample sizes included in clinical trials, and the structured environment of clinical trials versus patterns of use in general clinical practice. Indeed, the only way to completely avoid the occurrence of unanticipated risks after drug approval would be to stop approving new drugs. How the FDA deals with this uncertainty in benefit-risk assessment will profoundly affect treatment options for people with diabetes and for the health care professionals who care for them.

The challenges facing the FDA in the field of diabetes have been all too well illustrated in recent years. After many years of treating patients with a relatively limited pharmacological armamentarium, the past 20 years have witnessed the discovery of new drug targets and the development of new therapeutic options for people with diabetes. However, the risks of rapid advances have also become apparent. The introduction of thiazolidinediones was greeted with excitement because of their potential to change treatment paradigms. The subsequent withdrawal of troglitazone because of hepatotoxicity concerns made clear the

potential hazards of early adoption of new drugs.¹ In 2007, analyses suggesting that rosiglitazone increased cardiovascular event rates in people with type 2 diabetes² caused concern among both patients and physicians. Subsequent publications and regulatory reviews motivated by the rosiglitazone analyses fundamentally changed the landscape for diabetes drug development.

Cardiovascular events, including myocardial infarctions (MIs) and stroke, are major causes of mortality and morbidity in patients with diabetes. Thus, the risk that a therapy directed at improving glycemic control might increase the rate of these events is a legitimate concern. Traditional clinical development programs designed to establish the efficacy of a drug in lowering blood glucose concentrations are too small to definitively assess cardiovascular risk. Although these trials may not observe any risk, this is not the same as scientifically excluding an unacceptable increase in cardiovascular risk. The latter, more important, conclusion requires trials of sufficient size to accrue a sufficient number of cardiovascular events to statistically assess whether the associated risk is less than a predefined threshold.³⁻⁵ This was not done before the FDA's approval of rosiglitazone. Given the availability of alternative treatments for treating type 2 diabetes, it was suggested that this represented a structural failure in the drug approval process.⁶ In response, the FDA issued a formal guidance document in 2008 suggesting that explicit assessment of cardiovascular safety should be done as part of the development of all new drugs for type 2

diabetes regardless of their mechanism of action or preclinical and clinical evidence suggesting a possible increased cardiovascular risk.⁷ The FDA guidance established an upper limit of 1.3 for the relative risk of cardiovascular events, although a drug could be approved if the established relative risk at the time of approval was < 1.8 and the sponsor committed to a post-approval study to test the more stringent 1.3 threshold.

In recent years, this FDA cardiovascular risk guidance has been applied to the assessment of dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists, and sodium glucose co-transporter 2 inhibitors. For example, the post-approval safety study of saxagliptin has recently been published.⁸ This placebo-controlled, randomized trial included 16,492 patients followed for a median of 2.1 years and demonstrated a hazard ratio of 1.0 (95% CI 0.89–1.12) for the primary composite cardiovascular event endpoint. Of note, saxagliptin's development was associated with no preclinical or clinical signals of adverse cardiovascular effects, cardiovascular biomarkers were not adversely affected, and the mechanism of DPP-4 inhibitors would not have been predicted to have cardiovascular effects.

The philosophy behind the FDA cardiovascular guidance has been extended to insulin analogs. The FDA's final decision on the approval of insulin degludec has been delayed pending the results from a cardiovascular safety study.⁹ The design and execution of such large, blinded, comparator-controlled cardiovascular safety studies in patients with diabetes are extremely challenging, and this is especially true for a new insulin. The trial design must allow for optimal management of glycemic control, including titration of drugs and addition of new therapies, while maintaining blinding. This necessitates careful selection of treatment targets and comparator therapies in patients at high cardiovascular risk. Furthermore, comprehensive long-term follow-up is required to allow for interpretation of study outcomes.

In June 2013, the FDA Endocrinologic and Metabolic Drugs Advisory Committee met to reconsider the cardiovascular safety of rosiglitazone.^{10,11} The committee reviewed data presented by the FDA and others suggesting that the best estimate for the relative risk for cardiovascular events associated with rosiglitazone was < 1.3 and consistent with the FDA guidance. Thus, the signal that triggered the recent concerns about cardiovascular safety was not confirmed.

The FDA's response to the 2007 analyses suggesting increased cardiovascular risk associated with rosiglitazone was rational given the available information, but it was not without costs. Most directly, the publicity and label changes disrupted the care of millions of people with diabetes who decided to change therapies, resulting in unknown clinical and financial costs. Societal resources were diverted to deal with the litigation,¹² as well as the political and regulatory fallout from the analysis. The 2008 guidance on cardiovascular safety has delayed the development and increased the costs for new diabetes treatments. Furthermore, the focus on cardiovascular safety may have diverted attention from other safety considerations associated with specific drugs. For example, a study designed to better understand the risk of pancreatitis in patients being treated with incretin-based therapies would have different design features from one addressing potential cardiovascular risk and may yield more clinically relevant information. Looking forward, it is appropriate to ask whether there have been lessons from the recent experience in diabetes drug development that should be learned and whether the guidance itself requires refinement.

The FDA does not regulate the practice of medicine. However, how medicine is practiced may influence FDA decision-making. Ideally, the FDA could ensure that drug labeling provides prescribers with the available data and allows physicians and patients to decide on the use of the drug on a case-by-case basis. However, it is

far from clear that physicians are able to critically evaluate the data to optimize decision-making. The rapid, wide-scale use of drugs such as rofecoxib and rosiglitazone soon after their introduction, despite unclear advantages compared to existing therapies in most patients and uncertainty regarding their long-term safety, may legitimately give regulators pause when considering a new drug whose safety profile is incompletely established.

Thus, the availability of alternative therapies might raise the bar with respect to the required pre-approval safety data required for a new drug even if definitive safety data are lacking on the options that are already approved. This may have been the case for antidiabetes drugs; the FDA cited the "range of therapies" for type 2 diabetes in its cardiovascular safety guidance.⁷ Nonetheless, until physicians are able to critically review clinical trial data and then appropriately change their prescribing practices, use of a variety of mechanisms by the FDA to affect prescribing practices may be considered necessary. For example, if the FDA simply approved labeling that made no comment with respect to cardiovascular risk but simply included clinical trial data that are insufficient to exclude a doubling or tripling of MI risk, it is unlikely that physicians or patients would recognize this uncertainty in risk. This increases the importance of the FDA's judgment in its regulatory decision-making. Although the advisory committee process should be a valuable asset in formulating the required benefit-risk assessment, it is not clear whether this process is working optimally.^{13,14}

The safety principles enumerated in the FDA's 2008 guidance may influence drug development in other fields relevant to diabetes. The FDA Endocrinologic and Metabolic Drugs Advisory Committee has recommended requiring pre-approval cardiovascular outcome trials for all new obesity drugs, regardless of their mechanism of action or biomarker responses.¹⁵ The FDA has not officially adopted this recommendation, and perhaps the experience

with diabetes drugs suggests caution in the blanket implementation of this recommendation.

The net impact of this safety dynamic has likely been to decrease the therapeutic options for patients and physicians, increase costs for manufacturers of new diabetes treatments, and divert research capital away from diabetes and toward other therapeutic areas. Physicians, manufacturers, and regulators have all contributed to this environment, the net effect of which on public health is unclear. The experience of the past 10 years suggests that the effects may not have been uniformly positive, and renewed discussions should focus on how to better target pre- and post-approval definitive safety requirements.

Consideration of factors such as the biological plausibility for a drug's adverse effects, the clinical benefits associated with a new drug, and the totality of preclinical and clinical data (including positive vs. negative effects on cardiovascular biomarkers) should be used to inform regulatory decision-making rather than a one-size-fits-all policy for requiring safety studies. The one-size-fits-all approach to cardiovascular safety study requirements is unlikely to yield optimal allocation of resources or the most relevant data sets. Recalibration of the 2008 cardiovascular safety guidance to consider a broader array of potentially important safety considerations and to focus required pre- and post-approval formal safety assessments based on "probable cause" related to a drug's mechanism of action or available data may reinvigorate diabetes drug development and contribute to improved public health.

Acknowledgment

The author thanks Drs. William R. Hiatt and Kathy E. Sietsema for their helpful comments on this article.

References

- ¹From the Food and Drug Administration. *JAMA* 283:2228, 2000
- ²Nissen SE, Wolski K: Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 356:2457–2471, 2007
- ³Brass EP, Lewis RJ, Lipicky R, Murphy J, Hiatt WR: Risk assessment in drug development for symptomatic indications: a framework for the prospective exclusion of unacceptable cardiovascular risk. *Clin Pharmacol Ther* 79:165–172, 2006
- ⁴Fleming TR: Current issues in non-inferiority trials. *Stat Med* 27:317–332, 2008
- ⁵Fleming TR: Identifying and addressing safety signals in clinical trials. *N Engl J Med* 359:1400–1402, 2008
- ⁶Lazarus D: Avandia: when does a drug's harm outweigh its benefits? *Los Angeles Times* 1 July 2010. Available from <http://articles.latimes.com/2010/jul/01/business/la-fi-lazarus-20100702>. Accessed 25 November 2013
- ⁷U.S. Food and Drug Administration: Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes, 2008. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>. Accessed 2 October 2009
- ⁸Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mosenzon O, McGuire DK, Ray KK, Leiter LA, Raz I: Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med* 369:1317–1326, 2013
- ⁹Tucker ME: FDA rejects Novo Nordisk's insulin degludec. *Medscape* 11 February 2013. Available from <http://www.medscape.com/viewarticle/779077>. Accessed 25 November 2013
- ¹⁰U.S. Food and Drug Administration: Joint Meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees, 5 June 2013 [Transcript]. Available from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM369182.pdf>. Accessed 25 November 2013
- ¹¹U.S. Food and Drug Administration: Joint Meeting of the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees, 6 June 2013 [Transcript]. Available from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM369183.pdf>. Accessed 25 November 2013
- ¹²Feeley J, Kelley T: Glaxo said to pay \$460 million to settle Avandia damage suits. Available from <http://www.bloomberg.com/news/2010-07-13/glaxosmithkline-is-said-to-pay-460-million-to-settle-avandia-damage-suits.html>. Accessed 25 November 2013
- ¹³Brass EP: Assessing the benefit-risk for new drugs: are the FDA's Endocrinologic and Metabolic Drugs Advisory Committee and the Division of Metabolism and Endocrinology Products in sync? *Diabetes Care* 36:1823–1826, 2013
- ¹⁴Brass EP, Hiatt WR: Improving the FDA's advisory committee process. *J Clin Pharmacol* 52:1277–1283, 2012
- ¹⁵U.S. Food and Drug Administration: Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, 28–29 March 2012 [Minutes]. Available from <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303352.pdf>. Accessed 25 November 2013

Eric P. Brass, MD, PhD, is a professor of medicine at the David Geffen School of Medicine at the University of California, Los Angeles (UCLA) and director of the Harbor-UCLA Center for Clinical Pharmacology in the Department of Medicine at Harbor-UCLA Medical Center in Torrance, Calif.

Note of disclosure: The author is a consultant to Amarin, Amgen, Aveo, Bayer, BioMarin, Boston Scientific, Cangene, Catabasis, Endo, EnteroMedics, Galderma, GlaxoSmithKline, McNeil, Merck, Novartis, Novo Nordisk, QRx, Trius, and the University of Washington. In addition, he holds equity in Calistoga Pharmaceuticals and Catabasis.