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# EDITORIAL
# Raising the Bar for Diabetes Drug Approval

Diabetes mellitus (DM) is highly prevalent throughout the world. More than 20 million Americans are afflicted by this disease, and the incidence of DM continues to escalate secondary only to epidemic obesity throughout the world. Approximately 90% of patients with DM are characterized as having type 2 diabetes, with hyperglycemia driven by peripheral insulin resistance. Insulin resistance alters metabolism in a plethora of ways and leads to mixed dyslipidemia, hypertension, endothelial cell dysfunction, increased systemic inflammatory and oxidative tone, and increased risk for prothrombotic events. Secondary to the effects of glucotoxicity, lipotoxicity, and barotoxicity, patients with DM experience significant escalation in risk for atherosclerotic disease and its clinical sequelae (eg, myocardial infarction, stroke, sudden death) as well as for microvascular disease (eg, proliferative retinopathy, neuropathy, nephropathy). There is an urgent need to quell the rapid rise in DM and to elucidate evermore precise, mechanism-based pharmacologic means by which to control insulin resistance and hyperglycemia.

The US Food and Drug Administration (FDA) has based approval on glucose-lowering drugs (eg, sulfonylureas, thiazolidenediones, metformin, insulin) on such surrogate endpoints as capacity to reduce fasting blood sugar and hemoglobin A1c levels. To date, based on primary endpoints in prospective clinical trials, glucose lowering has not been shown to reduce the risk for acute cardiovascular events in a statistically significant manner, though trends toward reduction have been observed. Glucose lowering does, however, reduce the risk for development and progression of microvascular disease-related endpoints.

In July 2008, the FDA convened a panel of outside experts to address the issue of whether or not new antiglycemic drugs being considered for approval should meet more stringent standards. Some of the debate pivoted around a meta-analysis of rosiglitazone trials that suggested an increased risk for myocardial infarction and death. The shortcomings of the study have been broadly debated, and the study is hypothesis generating only. No prospective data are yet available to substantiate this finding. The panel ultimately recommended that new antiglycemic medications demonstrate no increase in risk for cardiovascular events in prospective, controlled clinical trials. In a reasonable move, the panel did not insist that these trials be completed prior to approval, but suggested that they be in place and ongoing at the time of approval.

Prospective clinical trials are critical to the way in which clinical guidelines and standards of care are developed. Clinical

trials aid in the delineation of who will be helped by certain interventions and by how much over specified periods of treatment. By evaluating whether or not a drug is harmful, there is no doubt that these studies will simultaneously serve to determine whether or not they actually reduce risk for cardiovascular disease. These are both important issues as they intimately impact the quality of patient care. Such trials will help to more clearly define whether or not certain interventions are worth the cost, on both human and economic levels.

There are, however, some other issues that warrant consideration as well. There is little doubt that this systematic approach will be extremely costly. Much of the argument on the need for demonstrating a lack of cardiovascular risk rests on a single meta-analysis that was clearly sensationalized in the press and not yet confirmed in a prospective clinical trial. To raise the bar on approval in this manner will escalate the cost of drug development significantly and likely adversely impact patent life. Will Congress allow for the extension of patent life when pharmaceutical companies face low or no widespread usage of a drug until long-term safety and efficacy studies are completed? Given the fact that bashing pharma is popular and garners votes, this is an unlikely possibility. Clinicians will not use drugs no matter how innovative if safety studies are "ongoing." If approval is delayed until long-term safety is established (which is not far fetched given the recent example of the drug Cordaptive), can a pharmaceutical company realistically recover its development costs? The cost to patients of new antiglycemic medications will almost certainly have to rise. The introduction of new drugs will also be slowed at a time when novel mechanisms in insulin resistance and glucose metabolism are being identified and therapeutically manipulated. Many companies will also likely bet that developing new drugs in DM will not be worth the risk. Few physicians who practice endocrinology or preventive cardiology doubt the clinical value of reducing insulin resistance and hyperglycemia.

Another issue also warrants some degree of scrutiny. When you ask clinical trialists, should more clinical trials be done, what do you think they are going to say? Clinical trialists make their living doing clinical trials. More will always be better. Always demanding more trials can come across as being somewhat self-serving. Some prominent clinical trialists also declare that they have distanced themselves from pharma and accept no consulting fees. Yet, some of these individuals and the institutions at which they work draw large sums of money from pharma for their services. Circular argument? Sometimes. Many clinical trials showcase certain technologies and biochemical parameters patented by investigators. Has this been looked upon as conflict of interest? It is time to ask the question. And, if certain pharma companies have not done certain types of clinical trials with certain technologies, are they disadvantaged when the time comes to seek regulatory approval? There is some suspicion of this as well. So, I suggest that the ante be upped still further. Instead of always simply looking with suspicion on pharma, perhaps some of the biggest, loudest, and most ardent advocates for more and ever more costly trials also undergo some critical scrutiny of their own. These are not trivial issues. Patients are always asking about what the future holds for new drugs. Unless debates are fair-minded and balanced with broad representation among many views, the answer will be an unfortunate "not much." To a significant degree, as medicine is increasingly politicized and the views of a few are snapped up by the press as Gospel, balance in clinical debates is rapidly becoming a thing of the past.