

industry; the reduced competition, which is likely to result, will endanger the availability of low-cost generic drugs in India and the developing world.

India has an obligation under domestic and international law to respect, protect, and fulfil the right to health of its people. To meet its health-care obligations India must guarantee the continued domestic production of generic drugs. International agreements that interfere with India's use of TRIPS flexibilities and require TRIPS-plus and other measures must, therefore, be resisted. Foreign investment in the drug industry must also be regulated to preserve India's fundamental and constitutional right to health for its citizens and those of the developing world.

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## Cardiovascular safety and diabetes drug development



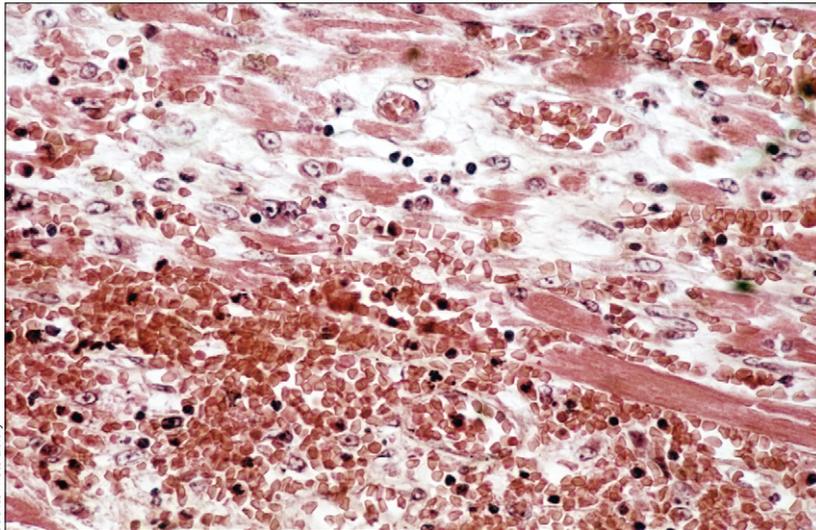
Recent innovations in the pharmacotherapy of type 2 diabetes are important, in view of the epidemic of type 2 diabetes and the individual and global economic costs of the disease. Although overall control of the disease has improved, more than 40% of patients on current therapies do not reach glycated haemoglobin (HbA<sub>1c</sub>) targets as suggested by clinical practice guidelines.<sup>1</sup>

The pathway for new drug development in diabetes traditionally involved 6–12-month studies that focussed on reduction of HbA<sub>1c</sub>. Historically, phase 3 clinical trials for a new antidiabetic agent involved 1000–3000 patients in total, a sample size that would be able to detect adverse events at the time of approval with frequency rates greater than 0.2%. However, emerging concerns about the long-term cardiovascular safety of diabetes drugs, caused in part by meta-analysis of clinical trials,<sup>2</sup> sparked a major shift in the diabetes drug-development model. After much deliberation, the US Food and

Drug Administration (FDA) issued new guidance for assessment of cardiovascular risk of drugs before and after approval.<sup>3</sup> The implementation of these guidelines will certainly enhance understanding of the safety of new antidiabetic agents. However, adherence to the guidelines will also add substantially to the cost and time needed to complete the approval process.

New diabetes drugs should offer clear advantages over available agents, and lower glucose via mechanisms associated with either neutral or beneficial effects on cardiovascular health. The most recently approved drug classes, agonists at the glucagon-like peptide 1 receptor (GLP-1R) (exenatide, liraglutide) and inhibitors of dipeptidyl peptidase 4 (DPP-4) (sitagliptin, vildagliptin, saxagliptin, alogliptin) seem to fulfil both criteria, although definitive cardiovascular outcome studies have not been completed. GLP-1R agonists improve glycaemia by stimulation of insulin secretion and inhibition of glucagon secretion and gastric emptying. Although thiazolidinediones, insulin

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Light-micrograph section through human heart after myocardial infarction  
Necrotic muscle fibres stain deeper red and do not show nuclei, compared with living muscle.

secretagogues, and insulin often lead to weight gain, GLP-1R agonists induce satiety, leading to weight loss in most patients. Unlike sulphonylureas, glinides, or insulin, GLP-1R agonists and DPP-4 inhibitors lower glycaemia in a glucose-dependent manner, thereby reducing the risk of hypoglycaemia. Importantly, the GLP-1R is expressed in cardiomyocytes, endothelial cells, macrophages, and in regions of the central and peripheral nervous system that regulate cardiovascular function. Hence GLP-1R activation produces direct and indirect actions on the blood vessels and heart in patients with diabetes.<sup>4</sup>

GLP-1R activation is directly cardioprotective in normal and diabetic animals. Interestingly, GLP-1(9-36), a metabolite of endogenous GLP-1, is also cardioprotective, which complicates the prediction of cardiovascular actions attributable to DPP-4 inhibitors and structurally distinct GLP-1R agonists.<sup>4</sup> Additionally, GLP-1R activation reduces postprandial intestinal lipoprotein secretion in rodents and human beings, and attenuates the development of atherosclerosis in mouse models of dyslipidaemia. GLP-1R is expressed on monocytes and macrophages, and agonists here reduce inflammation in normal, injured, and atherosclerotic blood vessels, and in hearts from animal models of diabetic cardiomyopathy. DPP-4 inhibition might also be cardioprotective; cardiovascular events were not increased in an analysis of phase 2 and 3 trials in patients treated with

saxagliptin.<sup>45</sup> Nevertheless, because rosiglitazone showed protective and anti-inflammatory actions in preclinical and proof-of-concept studies in human beings, healthy scepticism is needed about the available data on the cardiovascular actions of GLP-1R agonists and DPP-4 inhibitors.

What have we learned about the cardiovascular actions of GLP-1R agonists from clinical studies? Both exenatide and liraglutide reduce blood pressure and bodyweight in most patients.<sup>6</sup> A retrospective analysis of cardiovascular events in patients with diabetes treated with all available antidiabetic agents from 2005 to March, 2009, showed that being given twice-daily exenatide was associated with a statistically significant lowered risk of cardiovascular events and cardiovascular-related hospital admissions.<sup>7</sup> Although small increases in heart rate have been seen in some patients treated with exenatide or liraglutide, the clinical importance of this finding remains uncertain.

Patients' satisfaction and compliance with multiple daily injections are problematic; thus strategies designed to prolong the action of GLP-1R agonists and reduce the frequency of injection have appeal.<sup>8</sup> The first once-weekly formulation of exenatide seems to be more effective than twice-daily exenatide,<sup>9</sup> and a New Drug Application for exenatide once weekly was submitted to the FDA in May, 2009, with a revised new drug application resubmitted in April, 2010. The manufacturers received a second complete response letter from the FDA in October, 2010, with a new request for a thorough QT (tQT) cardiac study in patients exposed to high levels of exenatide. This request for new electrocardiographic data came as a surprise to most diabetologists. First, inter-individual variability in the pharmacokinetics of circulating exenatide after the once-weekly injection, with the potential for some individuals with renal impairment to have higher blood concentrations, has been known for over 3 years.<sup>9,10</sup> Results of the original tQT study, with single-dose exenatide, have been available since June, 2009, and do not seem to show a consistent dose-dependent QT abnormality. Moreover, a tQT study for liraglutide did not reveal a link between GLP-1R activation and QT prolongation.<sup>11</sup>

Lessons learned from rosiglitazone have led to earlier initiation of cardiovascular outcome studies for diabetes drugs,<sup>12</sup> including TECOS (sitagliptin, NCT00790205),

SAVOR-TIMI (saxagliptin, NCT01107886), LEADER (liraglutide, NCT00393718) and EXSCEL (exenatide once weekly, NCT01144338). These ongoing trials are adequately powered for safety and to show superiority rather than non-inferiority.

Assessment of the benefit–risk ratio for new drugs is challenging and the clinical community has high expectations for the efficacy and safety of new agents. Indeed, the recent report on cardiovascular outcomes with sibutramine exemplifies the risks inherent when establishing drug safety in populations at high risk for cardiovascular events.<sup>13</sup> Striking the balance between maximisation of efforts to ensure drug safety before approval in a transparent manner, without discouraging innovation and new drug development, seems more important than ever. All stakeholders will need to become increasingly thoughtful about risk tolerance and regulatory requirements for new agents if we are to foster an environment that encourages development of improved drugs to combat the diabetes epidemic of the 21st century. The challenges and uncertainties involved in development of drugs for metabolic disorders are further highlighted by the FDA's recent request for cardiovascular outcome studies as a condition for approval of the anti-obesity agent naltrexone plus bupropion.<sup>14</sup>

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