Executive Summary

Diabetes mellitus (commonly referred to as diabetes) is a serious and highly prevalent disease that has serious consequences, including death, if not well treated. In addition, it is also increasing in prevalence around the world due to increasingly affluent lifestyles and is commonly associated with the rise in obesity. In 2010, the global prevalence of diabetes was estimated to have reached 285 million and predicted to reach 438 million in 2030. The corresponding figures for North America were 37.4 million and 53.2 million and in Europe 55.2 million and 66.2 million.

There are two main forms of diabetes mellitus. Type I diabetes is an autoimmune disease caused by a progressive loss in the ability to produce insulin; this generally arises in early childhood. Type II diabetes is the more prevalent form, accounting for about 90% of all cases of diabetes, and is caused by an increasing loss of insulin sensitivity. Both conditions give rise to impaired glucose metabolism, with many serious consequences when the underlying condition is left untreated.

Treatment of diabetes relies on a number of therapeutic interventions. Type I diabetics require life-long treatment with insulin to compensate for their inability to produce sufficient quantities of the hormone. Type II diabetics can be treated with insulin but are more commonly first treated with one of a range of oral antidiabetic drugs to regulate insulin sensitivity and reduce hyperglycemia. However, the majority of type II diabetics are unable to control their glycemia by using just one such drug; the majority are treated with two or more of these drugs, and some 30% are also treated with insulin. A highly prevalent condition requiring treatment with multiple therapies thus generates a considerable demand for drugs, yet available agents still provide imperfect control of the disease. The medical need for newer, better drugs is widely recognized.

Exogenous insulin is required to control diabetes in all type I diabetics and some type II diabetics. Available insulin products fall into three categories: recombinant human insulins; modified insulins with both short and long durations of action; and non-recombinant products (often of animal origin), which are now infrequently used. Recent years have seen a progressive switch from the use of human insulin to the use of modified insulins, which offer more rapid absorption or more sustained insulin plasma levels and thus better control of the underlying disease. The market in such products is dominated by three companies: Eli Lilly, Novo Nordisk, and sanofi-aventis, and four products: insulin lispro (Humalog), insulin glargine (Lantus), insulin apart (NovoLog), and insulin detemir (Levemir), with collective sales of $11.5 billion in 2009.

Use of oral hypoglycemic drugs is essentially confined to type II diabetics, with many of the older agents now available in generic form. The oldest of these, metformin, is seen as an essential drug and is still widely used, both alone and in combination products. In 2009, it was one of the ten most prescribed generic drugs in the United States. The various classes of K_{ATP} channel modulators are also widely available as generic agents, with sanofi-aventis' glimepiride (Amaryl) and Novo Nordisk's repaglinide (Prandin) the only two branded products that maintain significant revenues. Three α-glucosidase inhibitors are available in some or all of the major markets; collectively, this group of agents has never proved to be a major success, with 2009 sales of just over $1 billion.

The most commercially successful group of oral hypoglycemic agents in recent years has been the glitazones (the PPARγ agonists), with 2009 sales of $4.9 billion. These revenues are increasingly dominated by Takeda's pioglitazone (Actos) due to concerns about the cardiovascular safety of rosiglitazone (GlaxoSmithKline's Avandia), leading to a collapse in revenues from that drug.

Other than modified insulin products, the other source of recent revenue growth for this market has been agents that target the incretin pathway: injectable agonists that activate GLP-1 receptors or DPP IV inhibitors that inhibit the peptidase that deactivates GLP-1. Two GLP-1 agonists are currently approved for use: exenatide (Byetta) and liraglutide (Victoza). Since Victoza was only approved in mid-2009 in Europe and January 2010 in the United States, only revenues from Byetta were significant in 2009 ($797 million).

Four DPP IV inhibitors are approved, but only one (Merck's sitagliptin [Januvia]) is a major product. Sitagliptin is approved in all major markets and had 2009 sales of $1.9 billion. Novartis' vildagliptin (Galvus, Equa) is approved in Europe and Japan and had 2009 sales of $180 million. Takeda's alogliptin (Nesina) was approved in Japan in April 2010. Neither vildagliptin nor alogliptin was approved by the FDA. Bristol-Myers Squibb and AstraZeneca's saxagliptin (Onglyza) was approved in both the United States and Europe in mid-2009 but had minimal sales impact ($24 million).

Since many type II diabetics require treatment with multiple drugs, combination products that offer enhanced convenience are also popular, especially those containing metformin. The three most popular such agents in 2009 were the combinations of metformin with sitagliptin (Janumet), pioglitazone (Actoplus Met), and rosiglitazone (Avandamet), collectively producing revenues of $1.3 billion.

In 2009, six key players dominated the $29 billion diabetes market, with GlaxoSmithKline's share (4%) decreasing while Merck's share (9%) rose. The four largest players were Novo Nordisk (24%), sanofi-aventis (17%), Takeda (15%), and Eli Lilly (12%).

Many agents are currently in development for the treatment of type I and type II diabetes. Although a few agents are directed at trying to cure the disease or suppress its development, the majority are directed at providing improved glycemic control. There is a heavy focus on particular targets thought to be of relevance, plus targets whose validity has been established (activation of GLP-1 receptors or inhibition of GLP-1 metabolism).

Many new insulin formulations are in development. Some seek to provide more sustained control of insulin levels, several are designed to provide more rapid elevation of insulin plasma concentrations, and considerable attention is being devoted to the development of formulations for delivery by routes other than injection. Three oral formulations and two (related) sustained-release formulations of insulin are currently in Phase III studies. Novo Nordisk's two formulations of insulin degludec appear most likely to progress to the market in the near future, with the extensive Phase III program scheduled to be completed by the end of 2010. In addition, an inhaled formulation (MannKind's Afrezza) and an ultra–fast-release formulation (Biodel's VIAject) have been filed for FDA approval.

Despite the FDA imposing additional demands on the toxicological evaluation of PPAR agonists before they progress to extensive clinical study, and the large number of failures of agents targeting one or more of these nuclear receptors, many PPAR agonists remain in clinical development; four (chiglitazar, balaglitazone, lobeglitazone, and aleglitazar) are in Phase III studies. Only Roche's aleglitazar (a PPARα/γ agonist) appears likely to proceed to regulatory filing in major markets. In 2009, Roche refocused the development of aleglitazar to a subset of type II diabetics, those with post acute coronary syndrome, in recognition of the poor competitive environment for PPAR agonists.

Many agents targeting the GLP-1 receptor are in clinical development for the treatment of type II diabetes. These include several alternative formulations of exenatide, with the extended-release formulation Bydureon (designed for weekly administration) currently awaiting FDA approval. Three GLP-1 analogs (dulaglutide, albiglutide, and taspoglutide), plus a modified form of exenatide (lixisenatide), are in Phase III studies. Regulatory submissions for Roche and Ipsen's taspoglutide were scheduled for 2011. However, investigation of an increased incidence of hypersensitivity reactions has delayed filing, with 2013 the likely filing date for all four of these peptides. All bar lixisenatide have been designed for weekly administration.

The development of orally administered DPP IV inhibitors remains an area of intense activity. Five agents in Phase III and four in Phase II studies seek to augment the four agents already approved in one or more markets. Boehringer Ingelheim's linagliptin (Ondero) is the most advanced of these and is scheduled for regulatory submissions at the end of 2010. The available data suggest that this may be the best-in-class agent. Mitsubishi Tanabe's teneligliptin is in more advanced development in Japan than in Western markets, and Phenomix recently lost its co-development partner for dutogliptin (Forest), suggesting that both these agents are likely to be submitted for FDA approval around the same time Takeda resubmits its NDA for alogliptin. Neither LG Life Sciences' gemigliptin nor Kowa's SK-0403 appear likely to be developed for Western markets. It is questionable whether any of the inhibitors in Phase II will have a viable commercial future.

The most advanced new approach to the treatment of diabetes is the development of inhibitors of the sodium-dependent glucose transporter SGLT2. Nine SGLT2 inhibitors are in clinical development; three of these are in Phase III studies. For the most advanced of these, Bristol-Myers Squibb and AstraZeneca's dapagliflozin, regulatory submissions are planned for the end of 2010. Canagliflozin is being developed by Mitsubishi Tanabe and Johnson & Johnson, with the latter having indicated its intention to file for approval in 2012. Astellas' ASP-1941 only commenced Phase III studies (in Japan) in May 2010, while Boehringer Ingelheim's BI-10773 commenced an extensive Phase II program in mid-2008.

Eleven activators of glucokinase are in Phase I or II studies. AstraZeneca's AZD-1656 is apparently the most advanced, with regulatory submissions currently planned for 2015. Roche had progressed one compound to advanced Phase II studies, but chose to abandon its effort in the area for undisclosed reasons. A similar number of 11β-hydroxysteroid dehydrogenase-1 (11β-HSD1) inhibitors are in Phase I or II studies. Four are in Phase II studies, with Roche comparing its two candidates RG-4929 and RG-7234 in a head-to-head study that commenced in mid-2009. Incyte had successfully completed a Phase IIb study with INCB-13739 by mid-2009, but further development is awaiting a partner or licensor. Japan Tobacco's JTT-654 is also in Phase II studies.

A number of other targets have recently attracted a considerable degree of interest including the GPCRs GPR119, FFA1, and TGR5. Most prominent among these is the development of GPR119 agonists, with OSI's PSN-821, GlaxoSmithKline's GSK-1292263, and Metabolex' MBX-2982 all progressing to Phase II development in 2009. The development of agonists selective for the FFA1 receptor is also increasing: Takeda's TAK-875 commenced Phase II studies in December 2009, while Intercept is the first company to confirm that it is developing TGR5 agonists such as INT-777. Inhibitors of a number of metabolic enzymes are also attracting interest, although the glycogen phosphorylase inhibitor GSK-1362885 is the only such agent in Phase II development. GlaxoSmithKline is also developing a number of its SIRT1 inhibitors for the treatment of diabetes, with both GSK-2245840 and GSK-184072 in Phase II development. A number of other approaches are being investigated by diverse companies, with either a single small molecule directed at a single target or where their mode of action has yet to be disclosed. Many of these are being developed by smaller companies, but Transition Therapeutics in collaboration with Eli Lilly has progressed the gastrin analog TT-223 into Phase II development. A number of biological products are also being developed, with Eli Lilly evaluating a number of such agents. But the majority of biological agents appear to be more suitable for use by subsets of diabetics rather than the majority of diabetics.

All of the six major players in the diabetes market have a significant number of new agents in clinical development. sanofi-aventis' pipeline is strongly dependent on in-licensed products, while Merck is focused on developing combinations of sitagliptin and exploring several earlier-stage projects. Novo Nordisk's pipeline comprises multiple insulin and GLP-1 agonist-based formulations, reflecting its focus on non–small-molecule approaches. Eli Lilly, GlaxoSmithKline, and Takeda all have broad and diverse development pipelines.

Among the major companies that currently lack a significant presence in the diabetes market, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, and Roche all have broad development pipelines, with each company pursuing multiple targets for the treatment of diabetes. Many smaller companies are active in developing agents for the treatment of diabetes, with Metabolex and TransTech Pharma having the most substantial pipelines with respect to number of NCEs, development status, and range of targets.

The multiplicity of agents currently in development for the treatment of diabetes and the continued growth in the incidence of type II diabetes will be the key factors for the growth in value of the diabetes market over the next few years. But their impact will be blunted by the loss of revenues from established products, as generic substitutes for a number of established products (most notably pioglitazone) become widely available.

The period 2010–2015 should see a number of new agents reach the market, with a steady rate of NDA filings expected between 2010 and 2013. Four products are currently awaiting FDA approval, including Bydureon, with a further five filings expected in 2010 and five more each in 2011 and 2012, while 2013 is expected to see a surge in filings for SGLT2 inhibitors and GLP-1 agonists. The anticipated filings include what appear to be best-in-class GLP-1 agonists and DPP IV inhibitors, as well as the first three SGLT2 inhibitors and new insulin formulations. Due to the impact of such developments and the steady uptake of recently approved DPP IV inhibitors and GLP-1 agonists, the value of the diabetes market should grow steadily during the period 2009–2014, at a compound annual growth rate of 4.7%.