Executive Summary

Protein kinases are a large family of proteins that have now became firmly established as a major class of drug targets for the pharmaceutical industry. The sequencing of the human genome has led to the identification of 518 protein kinases encoded within it: the human kinome. This constitutes one of the largest classes of potential drug targets for the pharmaceutical industry, with the number of kinases exceeding the number of G protein–coupled receptors in the human genome.

Until the late 1980s, it was thought that protein kinases would not be tractable drug targets, both because of the presumed need to compete with adenosine triphosphate (ATP) and because it was assumed that target selectivity would be impossible to achieve. Since then, considerable progress has been made, and the past few years have seen a number of kinase inhibitors reach the market. By the end of 2006, 7 kinase inhibitors had reached the market, 3 in the period from December 2005 to December 2006, and their collective sales exceeded $4 billion. A further 3 kinase inhibitors have been approved in 2007.

These developments reflect the explosion in the number of kinase inhibitors that have entered clinical development in recent years, with over 150 inhibitors currently reported to be in clinical development and many more in preclinical development. Kinase inhibitors now constitute a significant fraction of most major pharmaceutical companies' pipelines as well as an area of focus for many biotechnology companies. The increased interest in this class of targets reflects both on the recognition of how to identify selective protein kinase inhibitors and on their perceived potential as offering many new approaches to the treatment of cancer, generally providing well-tolerated oral therapeutics.

The global increase in the prevalence of cancers and the recognition that the oncology market has traditionally been underexploited by the pharmaceutical industry have provided a major incentive for the development of new agents for the treatment of cancer. Since many of the identified protein kinases have been implicated in various cancers, this increases the interest in pursuing their development for oncology indications. Although direct kinase inhibitors accounted for only 7% of the value of the oncology market in 2006, their increasing availability and use are likely to be one of the major drivers of growth in the overall oncology market, predicted by Bayer to reach $100 billion in 2009.

The 518 identified protein kinases have been grouped into a total of 8 families, based on their structures. The 388 serine-threonine kinases fall into 5 families: AGC, CAMK, CMGC, CK1, and STE, with the 90 threonine kinases falling into 2 families, the TK (tyrosine kinase) family of 58 kinases and the TKL family, with 40 atypical kinases highly structurally distinct from the remainder. Of the AGC family, only the AKT and PKC subfamilies have currently attracted much interest, while interest in the CAMK, STE, or the small CK1 families is even less. In contrast, many members of the CMGC family have attracted considerable attention; this family includes cyclin-dependent kinase (CDK), glycogen synthase kinase 3 (GSK3), p38, and JNK kinases. The TK family is also a source of great effort, both the receptor-linked kinases, such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor (PDGFR), and the non-receptor Src subfamily. Certain members of the TKL family, such as Raf and the STKR subfamilies, are also a source of great interest.

Imatinib (Novartis' Gleevec) was the first approved kinase inhibitor and is currently the most commercially successful, with sales reaching $2.5 billion in 2006. Erlotinib (OSI/Roche/Genentech's Tarceva) is also developing into a major product and appears likely to reach blockbuster status in 2007. Two of the more recently approved agents, sorafenib (Bayer's Nexavar) and sunitinib (Pfizer's Sutent), were both initially approved for the treatment of renal cell carcinoma, and 2 other agents, dasatinib (Bristol-Myers Squibb's Sprycel) and nilotinib (Novartis' Tasigna), are both primarily directed toward treating patients who are resistant to imatinib; lapatinib (GlaxoSmithKline's Tykerb) is approved for the treatment of breast cancer.

Most major pharmaceutical companies now have several kinase inhibitors in clinical development, although the major Japanese companies still show little interest in this class of targets. AstraZeneca, a pioneer in the development of kinase inhibitors, currently has the largest number (12) of kinase inhibitors in clinical development, while Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Novartis, Pfizer, and Roche all have between 4 and 8 kinase inhibitors in development. All of these companies plus Merck are also highly active in filing patents claiming kinase inhibitors.

A number of kinases are very popular targets, with the most intense interest focused on agents targeting the tyrosine receptor kinases EGFR, ErbB2, and the VEGFRs. Other kinases attracting considerable attention in the search for new agents for the treatment of cancer are the Aurora kinases and cyclin-dependent kinases. The commercial success of imatinib has prompted considerable interest in the identification of broader-spectrum inhibitors of Bcr-Abl and the mutant, imatinib-resistant forms, while targets such as phosphoinositide kinase 3 (PI3K) and Akt are attracting increasing attention.

In addition to ongoing studies of approved kinase inhibitors seeking line extensions, a further 11 are currently in Phase III studies. Eli Lilly filed for approval of the protein kinase C-beta (PKCβ) inhibitor ruboxistaurin, but its NDA in February 2006 was rejected by the FDA. Only 3 NDA filings for kinase inhibitors are anticipated in 2008: Cephalon's lestaurtinib, an Flt3/JAK2 inhibitor, for the treatment of acute myeloid leukemia; GlaxoSmithKline's multikinase inhibitor pazopanib for the treatment of renal cancer; and AstraZeneca's vandetanib, a VEGFR/EGFR inhibitor, for the treatment of non–small cell lung cancer. No filings are currently anticipated in 2009, while a further 3 filings are expected in 2010: AstraZeneca's VEGFR inhibitor cediranib for non–small cell lung cancer; sanofi-aventis' alvocidib, a CDK inhibitor, for the treatment of chronic lymphocytic leukemia; and Eli Lilly's PKCβ inhibitor enzastaurin for the treatment of B-cell lymphoma.

More than 130 kinase inhibitors are currently reported to be in either Phase I or Phase II clinical development, with 47 in Phase II studies. Inhibitors of p38 kinase account for 11 of the inhibitors in Phase II studies, almost all for the treatment of rheumatoid arthritis, and a further 9 are in Phase I development. Other classes of inhibitors where multiple compounds are in Phase II studies include Abl (4), VEGFR (9), and insulin-like growth factor receptor (IGFR; 3). Although many Aurora and CDK inhibitors are in development, few have yet progressed beyond Phase I studies. The development of GSK3 inhibitors for the treatment of Alzheimer's disease represents the first potential use of kinase inhibitors for a central nervous system indication, but both inhibitors in development have yet to progress beyond Phase I studies.

The number of kinase inhibitors in clinical development ensures that over the next 10 years a significant number of such agents will reach the market. The majority of these will be for oncology indications, reflecting the more acute nature of the disease, and thus greater tolerability of potential side effects, and the current emphasis on developing kinase inhibitors for cancer indications. The development of kinase inhibitors for chronic indications necessitates better target selectivity to minimize side effects and helps to explain why 20 years of research and development on p38 inhibitors have led to very few compounds progressing (at best) beyond early Phase II studies. Nevertheless, success is likely to be achieved eventually.

This report reviews the considerable array of drug development efforts directed at kinases and provides profiles of the activities of the major companies as well as the kinase inhibitors in development, and some of the specialist companies active in the field, with regard to drug development or technology provision. It assesses the potential impact of the more advanced kinase inhibitors, which offer significant market potential, and discusses some of the technical challenges faced in developing such inhibitors. It concludes with commentaries from leading experts in the field.