

# Executive Summary

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Kinases are a large family of proteins that have now become 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.

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 sufficient 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 2008, 13 kinase inhibitors had reached the market, and their collective sales were approaching \$8 billion. In 2009, two kinase inhibitors were approved for canine use; a third, already approved as an immunosuppressant, was approved with a different trade name for the treatment of cancer; and a fourth was approved for the treatment of renal cell carcinoma.

These developments reflect the explosion in the number of kinase inhibitors that have entered clinical development in recent years, with around 200 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 the recognition of how to identify selective protein kinase inhibitors and their perceived potential to offer many new approaches to the treatment of cancer, generally providing well-tolerated oral therapeutics.

The global increase in the prevalence of cancers, and the increasing recognition of the therapeutic and commercial opportunities offered by new oncology treatments, has provided a major incentive for the pharmaceutical industry to pursue the development of new agents for the treatment of cancer. As many of the identified protein kinases have been implicated in the development of various cancers, much attention has been devoted to their development for oncology indications. Although direct kinase inhibitors accounted for only 16% of the value of the oncology market in 2008, their increasing availability and use is

likely to be one of the major drivers of growth in this market, which is predicted to reach \$85 million in 2013 and is one of the few segments of the pharmaceutical market that is expected to grow significantly in the near to medium term.

The 518 identified protein kinases have been grouped into a total of seven families, based on their structures. The 388 serine-threonine kinases fall into five families: AGC, CAMK, CMGC, CK1, and STE; the 90 tyrosine kinases fall into two families: the TK (tyrosine kinase) family of 58 kinases and the TKL (tyrosine kinase-like) family of 32 kinases; and 40 atypical kinases are 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, on 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 the Raf and STKR subfamilies, are also a source of great interest.

There is strong evidence of the involvement of many of these kinases in cancer, with tyrosine receptor kinases highly prominent, while only a small number of kinases have been implicated in other conditions. The regulation of cancer cell growth is often modulated by multiple kinases acting both in independent pathways and in concerted signaling cascades, but current knowledge does not clearly identify which kinases are the more critical in such pathways. A number of kinases have been highlighted as being of critical importance in inflammatory diseases, with p38, JAK2, and certain isoforms of PI3K and PKC particularly significant, and the role of mTOR in immune regulation is well documented. Even fewer kinases appear to be implicated in the development of metabolic, CNS, or cardiovascular diseases, but GSK-3 has been implicated in both metabolic and certain CNS disorders while both ROCK and SGK1 have been implicated in cardiovascular diseases.

Imatinib (Novartis' Gleevec) was the first approved kinase inhibitor and is currently the most commercially successful, with sales reaching \$3.7 billion in 2008. Erlotinib (OSI/Roche's Tarceva) is also a major product and generated revenues of \$1.1 billion in 2008. Sunitinib (Pfizer's Sutent), with 2008 revenues of \$865 million, is currently the only other approved kinase inhibitor that might achieve blockbuster status in 2009, while sales of sorafenib (Bayer's Nexavar) were \$599 million in 2008. None of the four approved agents that target mTOR achieved revenues in excess of \$400 million, while sales of fasudil (Asahi's Eril) for the treatment of brain hemorrhage were small. Sales of these kinase inhibitors are currently dwarfed by those of the recombinant products that target HER2, EGF, and VEGF, with collective 2008 revenues of \$12 billion.

In the latter half of 2009, we identified 201 small-molecule kinase inhibitors as being in active clinical development, an approximately 60% increase on the number in development in 2006, with further inhibitors expected to enter development by the end of 2009. Of these 201, two (the EGFR/VEGFR inhibitor vandetanib and the pan-VEGF inhibitor pazopanib) had been filed for approval (pazopanib [GlaxoSmithKline's Votrient] was subsequently approved for renal cell carcinoma), while a further 18 were in Phase III development and 71 in Phase II studies. Oncology indications accounted for 159 of the 201 inhibitors including 18 of those in Phase III and 52 in Phase II. Inflammatory indications accounted for nearly half of the kinase inhibitors not being developed for treating cancers, with 12 being developed for the treatment of rheumatoid arthritis, including the JAK3 inhibitor CP-690550 in Phase III.

Of the other kinase inhibitors in Phase III, three are expected to be filed in 2010, the CDK inhibitor alvocidib, the mTOR inhibitor ridaforolimus, and the PDGFR/VEGFR inhibitor BIBF-1120; the PKC inhibitor midostaurin in 2011; and CP-690550 and the FGFR/VEGFR inhibitor brivanib in 2012. Eli Lilly has already filed, unsuccessfully, for approval of the PKC inhibitor ruboxistaurin and now anticipates delaying filing of enzastaurin until 2013.

A total of 71 kinase inhibitors are currently reported as being in Phase II studies, just 19 of them for non-oncology indications. Eighty-nine of the 110 kinase inhibitors reported to be in Phase I development are being developed for oncology indications. Certain kinases or kinase families account for a considerable number of these. In addition to five in Phase III that target EGFR and/or ErbB2, a further 18 such inhibitors are in Phase I or II studies. In addition to the five VEGFR inhibitors in Phase III, a further eight are in Phase I or II studies as are 11 multi-kinase inhibitors that target various kinases including those activated by VEGF. In contrast, relatively few small-molecule inhibitors in development target Flt3, IGFR, or FGFR.

The PI3K/Akt/mTOR/S6K cascade is attracting increasing interest with many inhibitors now having entered clinical development, nearly all of which are in Phase I or II studies. Fifteen isoform-selective and non-selective inhibitors of PI3K are in development for various indications, six mTOR inhibitors are in development including three that inhibit both TORC1 and TORC2, and eight Akt inhibitors are in Phase I or II for the treatment of cancer. Eight inhibitors of the Raf kinases are in early stage clinical development, while 12 inhibitors of MEK kinases are in development for both oncology and inflammatory indications. Kinases involved in the cell cycle account for a significant proportion of the small-molecule inhibitors in development for the treatment of cancer. In addition to the Phase III compound alvocidib, nine other CDK inhibitors are in clinical development, plus five Chk1 inhibitors and six PLK inhibitors.

Inhibition of p38 accounts for 12 or 13 of the kinase inhibitors in development, most of these p38 inhibitors being developed for the treatment of inflammatory disorders. Rheumatoid arthritis is still a preferred indication despite clinical results with pamapimod suggesting that any clinical benefits are a short-term effect. There has been a recent

resurgence of interest in the development of isoform-selective PKC inhibitors, but currently only four are in earlier-stage clinical development compared to the three that have progressed to Phase III. The role of Aurora kinases in cellular mitosis has led to considerable interest in their inhibition, and 14 inhibitors of Aurora 1 and/or Aurora 2 are now in Phase I or II development.

Eight c-Met inhibitors are now in clinical development, plus three recombinant products targeting HGF. BMS-907351 and PF-2341066 both recently entered Phase III studies, while ARQ-197 is in Phase II. Five ROCK inhibitors are in clinical development for the treatment of glaucoma and a sixth for the treatment of erectile dysfunction. The Src family kinases are still proving difficult to target specifically, although six inhibitors of various members of the family are currently in clinical development.

Four kinases are prominent inflammatory targets in addition to MEK and p38; IKK2, JAK3, Syk, and Zap-70. Four IKK2 inhibitors, two Syk inhibitors, and three JAK3 inhibitors are in clinical development, with inhibitors of both Syk and IKK2 in Phase II studies in addition to the JAK3 inhibitor CP-690550 in Phase III. An increasing number of inhibitors of diverse other kinases are now being described, with a number having reached early clinical development.

Although kinases are now established as a major class of potential new drug targets, there are considerable discrepancies in the level of pipeline activities between the major companies. Several (AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Novartis, and Pfizer) are especially active, while others, especially the Japanese majors other than Takeda, currently have few kinase inhibitors in development. The perceived tractability of kinases as drug targets has led to an increasing number of emerging companies focusing on the development of kinase inhibitors. Many of these are developing kinase inhibitors in partnership with major companies, while others may be seen as potential acquisition targets.

Of the smaller companies, Array BioPharma and Exelixis stand out as having large pipelines of kinase inhibitors, some of which are being developed in partnership with major companies. Rigel, with one major partnership with Pfizer, and Nerviano Medical Sciences, currently with no partnerships, also both have significant kinase inhibitor clinical pipelines. The desire to extensively profile kinase inhibitors has led to the emergence of a number of service companies that offer such services. Some of these, such as Ambit Biosciences, are also starting to develop kinase inhibitors independently while others, e.g., Upstate, have become part of larger service companies.

The period from 2008 to 2015 should see a number of additional kinase inhibitors reach the market. GlaxoSmithKline's pazopanib (Votrient) was FDA approved for renal cell carcinoma in October 2009, but commercial success will probably depend upon the outcome of a head-to-head study against sunitinib. AstraZeneca's cediranib, with a similar profile and superior potency, is expected to be filed for colorectal cancer in late 2010. Two other multi-kinase inhibitors, Amgen's motesanib and Pfizer's axitinib, may also reach the market by 2014.

AstraZeneca's vandetanib is a relatively selective VEGF inhibitor and was filed for approval for the treatment of non-small-cell lung cancer in July 2009. 2010 is expected to see several filings in addition to that for cediranib: Boehringer Ingelheim's multi-kinase inhibitor BIBF-1120 for the treatment of non-small-cell lung cancer; Incyte's JAK1/JAK2 inhibitor INCB-18424 for the treatment of myelofibrotic disorders; Merck & Co. and Ariad's mTOR inhibitor ridaforolimus for sarcoma; sanofi-aventis' CDK inhibitor alvocidib as a third-line treatment for leukemia; and possibly Cephalon's Flt3 inhibitor lestaurtinib for acute myeloid leukemia. Filings are expected in 2011 and 2012 for Novartis' PKC inhibitor midostaurin for aggressive systemic mastocytosis and acute myeloid leukemia, respectively. 2012 is expected to see two other filings: Bristol-Myers Squibb's multi-kinase inhibitor brivanib for the treatment of liver cancer and Pfizer's JAK3 inhibitor CP-690550 for the treatment of rheumatoid arthritis, both of which appear to have significant commercial potential.

The outcome of these developments should see the annual revenues generated by kinase inhibitors approximately doubled by 2015, from the near \$8 billion generated in 2008. Much of the growth will be driven by increased uptake of the currently approved products. Although CP-690550 has the potential to become a major product, its impact will be modest before 2015, while both vandetanib and BIBF-1120 (because of their primary indication) clearly have significant potential.

Forecasting the longer-term outlook for kinase inhibitor revenues is more problematic. Early clinical promise is frequently not replicated in larger clinical studies. The large number of kinase inhibitors in Phase II in 2009 should ensure that the period between 2015 and 2020 sees a steady flow of new kinase inhibitors approved for use. This will ensure the continued growth of commercial revenues from kinase inhibitors, although much of the growth will be driven by those approved by 2015. A number of additional agents will be approved for the treatment of cancer, and there appear to be reasonable prospects for one or two kinase inhibitors (in addition to CP-690550) being approved for the treatment of chronic inflammatory conditions. By 2020, small-molecule kinase inhibitors should collectively be generating annual revenues of > \$25 billion.

