Accurately predicting the future success of a novel therapeutic compound in today’s burgeoning oncology market is perhaps best achieved by consulting a really good crystal ball. Alternatively, R&D managers can plot a drug’s strengths and weaknesses against the emerging universe of insights into the molecular basis of disease and factor in the challenges of increasingly rigorous data review, high drug development price tags, unpredictable development timelines, and a wary post-launch reception from cost-cutting reimbursement regulators in every major pharmaceutical market.

The price of developing a new drug may run close to $870 million, and while blockbuster profits are possible, manufacturers should expect a long wait: novel compounds that do boast the efficacy and safety to achieve commercialization often take more than a decade to accomplish this goal. And yet, every so often, a few noteworthy new entities emerge to re-energize treatment algorithms and heat up the pharma industry — while the potential for healthy profits warms the hearts of those who nurtured the drug through its expensive early years.

Two such entities — sunitinib (Pfizer’s Sutent) and sorafenib (Bayer’s Nexavar) — appear poised for such success. Capitalizing on rational drug design and a savvy strategy of launching into a market of high unmet need and a low bar for upsetting the previous standard, these agents are using the niche indication of renal cancer as their platform to amass clinical trials data, gain momentum, and establish the marketing resources to perhaps climb the pyramid of major indications and achieve multi-year blockbuster sales. So how will they do this?
**Sunitinib**

Sunitinib, approved in the US and Europe in 2006 for the treatment of advanced renal cell carcinoma (RCC) and for the treatment of gastrointestinal stromal tumour (GIST) after disease progression on or intolerance to imatinib (Novartis’s Gleevec/Glivec), is an oral multi-kinase inhibitor, acting against cell proliferation pathways such as overexpression of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These approvals were soon followed by proof of its superiority as a first-line therapy in metastatic RCC (mRCC), over the standard cytokine therapy, interferon, with significantly better progression-free survival and response rates. This result, announced at the 2006 American Society of Clinical Oncology (ASCO) annual meeting, changed the practice of mRCC management and established sunitinib as the new standard of care for these patients. EU approval for the first-line treatment of advanced and/or mRCC was granted in January 2007.

Additional early trials also suggest a role for sunitinib in mRCC and GIST in combination with or as salvage therapy after the failure of other small molecule products, and trials of the drug in combination with VEGF-targeting drugs are ongoing in additional indications including breast, lung and colorectal cancer.

Sunitinib’s uptake in its first years on the market for its present niche indication is encouraging. Is its commercial success guaranteed? Much depends on the level of competition and positioning of its strongest current competitor, sorafenib.

**Sorafenib**

Sorafenib is an oral, multi-kinase inhibitor approved in late 2005 in the US and in July 2006 in Europe for the treatment of advanced RCC. It has also received attention for an apparent strong role in liver cancer — a pivotal Phase III study evaluating its use as a single agent in patients with advanced disease was halted early when the trial achieved its endpoints as of interim analysis. Bayer and its drug development partner Onyx now plan to file for regulatory approval in the US and EU in liver cancer, meaning that sorafenib is likely to establish itself in its second indication roughly one year after being on the market for its primary indication of advanced RCC — an impressive achievement.

Sorafenib is also being evaluated in metastatic melanoma, non-small cell lung cancer, breast and other cancers.

**Why was renal cancer the right move?**

How much of a drug’s ongoing commercial success is attributable to its primary indication? In the case of sunitinib and sorafenib, launching in RCC will likely prove to be a savvy and lucrative decision. Granted, market entry into niche tumours — treatments for advanced RCC account for approximately 2% of all cancer treatments each year, compared to 14% for breast cancer and 16% for colorectal cancer — is a less common approach for drug launches than is launch into a small segment within a broader indication.

Sunitinib and sorafenib certainly had a choice of indications. Sunitinib, for example, was designed specifically for potency against VEGF receptors and PDGF receptors, angiogenic proteins that are over-expressed in many solid tumour types, including lung, breast, gastrointestinal tract, bladder, pancreas, and ovarian cancers. VEGF is also expressed in a wide variety of lymphomas and leukaemias. Sunitinib demonstrated robust antitumour activity in preclinical studies, resulting in tumour growth inhibition and regression in models of colon cancer, non-small cell lung cancer, melanoma, renal carcinoma, and squamous cell carcinoma. Clinical activity was demonstrated in neuroendocrine, colon and breast cancers in Phase II studies. Sorafenib showed broad-spectrum antitumour activity in colon, breast and non-small cell lung cancer models. Many of these indications feature far larger patient populations and much greater visibility than does renal cancer.

However, advanced RCC and mRCC dangle a few items of bait that the more populous and competitive indications cannot match. First, advanced and metastatic RCC feature tremendous unmet need. A meagre 20% of mRCC tumours respond to standard cytokine therapy, thus rendering 80% of patients without any effective treatment. In addition, up to 50% of patients with earlier-stage cancer at diagnosis relapse despite surgery, and an alternative to palliative therapy for these patients is desperately needed. Add in the increasing incidence of RCC, plus the fact that mRCC is a level playing field for drug therapy — currently no single standard drug dominates the market — and RCC becomes a lucrative commercial opportunity and will likely serve as a very strong platform for escalating the uptake of sunitinib and sorafenib.
The clinical value of sorafenib and sunitinib in later-stage RCC is evident in their steady uptake in the US and EU since their approval (Figure 1).

Prior to their availability, very few mRCC patients received second-line systemic therapy — EU data show that in 2005 only one in four patients on first-line therapy moved to second-line and fewer than one in 10 received third-line therapy.8 With the launch of sunitinib and sorafenib in the EU, the use of chemotherapy in these patient groups doubled, with the drugs being given to the additional patients. Today, third-line treatment of mRCC consists almost entirely of sunitinib and sorafenib given as single agents. The move into first-line, albeit on trial, was already appearing in 2006; sunitinib’s recent licence in this area will only serve to increase this penetration.

A drug that appears to demonstrate efficacy across indications is well-positioned to be quickly accepted

These prescribing patterns translated into global sales in 2006 of $175 million for sunitinib and $39 million for sorafenib.9 Although these figures appear modest compared with those of other rationally designed drugs launched in niche indications — imatinib achieved sales of $220 million in its first year of launch for chronic myelogenous leukaemia, and Erbitux $307 million for colorectal cancer10 — one can hypothesize that this is only the beginning for sunitinib and sorafenib, particularly given the status of their market now, versus the way in which they are likely to shape it going forward.

Creating future potential

Closer examination of the current treatment algorithm for patients with mRCC receiving first-line drug therapy in the Top 5 pharma markets in Europe (France, Germany, Italy, Spain and the UK) shows that, while sunitinib is represented among treatments for the 17% of patients with stage IV disease receiving drug therapy first-line, such use is very limited11. This is surprising considering that a Phase III trial comparing sunitinib to interferon as first-line therapies in patients with mRCC showed significantly better progression-free survival and response rates for sunitinib. Over the next three to five years, accordingly, one could expect sunitinib in this patient pool to become the most prevalent chemotherapy for patients previously treated with cytokines. If sunitinib were prescribed to, say, 80% of mRCC patients receiving drug therapy first-line, this would translate into an estimated 14000 patients receiving the drug as opposed to the current 300012 — creating the potential to more than triple sales within this patient subset alone.

Sorafenib has also yet to come close to its potential — IMS Oncology Analyzer data suggest that currently it sees essentially no use as a second- or third-line regimen for patients previously treated with systemic therapy. Yet, in its major Phase III trial in mRCC patients who had received one prior systemic therapy (cytokine or other), it was shown to significantly double progression-free survival versus placebo across all patient subsets. One potential scenario over the coming years is that sorafenib takes over a percentage of sunitinib’s 41% presence in second-line mRCC.

Equally there is likely to be room for both drugs in the mRCC market because sequential drug administration may prove to be more effective than “either/or” therapy. Furthermore, their success in mRCC will in all likelihood increase the percentage of patients treated with chemotherapy in general. Again, only a small minority of mRCC patients currently receive chemotherapy (Top 5 Europe) as a first-line treatment, and in the second-line and third-line chemotherapy is also underused compared with drug therapy for many other solid tumours — presumably attributable to the fact that until sunitinib and sorafenib came along, no systemic drug therapy had proven more effective than another, and traditional cytokine therapy for mRCC was associated with significant adverse side effects. However, both sunitinib and sorafenib have been moderately well-tolerated, potentially increasing physician and patient willingness to use them. Accordingly, and as is consistent with emerging treatment dynamics for other tumour types, it is expected that the percentage of patients receiving systemic therapy with agents such as sunitinib and sorafenib will increase in first- and second-line treatment algorithms, as well as in third-line.

Finally, sunitinib and sorafenib are currently indicated for use only in the approximately 28% of patients diagnosed with advanced or metastatic RCC. However, the oncology community is increasingly identifying a role for some types of chemotherapy in treating early-stage solid tumours, depending on a range of prognostic and other factors.

Lessons for the future

The emerging legacy of sunitinib and sorafenib appears to be one of maximizing rational drug design within niche markets featuring high unmet need, and quickly expanding to additional, equally attractive and attainable indications.

As in the case of sorafenib, particularly, a drug that appears to demonstrate efficacy across indications is well-positioned to be quickly accepted by physicians, regulatory bodies, and reimbursement organizations. Furthermore, all of these groups can be expected to consider data built via one indication when evaluating the drug’s role in another, saving on development time and expenses.
From the pharmaceutical marketing perspective, it may be faster, easier and cheaper to promote one drug across several indications than to promote an individual drug for each indication. Launching into a market that can accommodate newcomers and welcome them with premium pricing would seem the basis for a successful strategy. By updating clinicians’ attitudes to the value of chemotherapy for advanced disease and capitalizing on new molecular identities to design advantageously sequenced drug therapy, the manufacturers of sunitinib and sorafenib are showing the industry one pathway to commercial success.

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IN BRIEF
The route to commercial success appears to be maximizing rational drug design within niche markets featuring high unmet need that can accommodate newcomers and welcome them with premium pricing, and quickly expanding to additional, equally attractive and attainable indications. A drug that demonstrates efficacy across indications is well-positioned to be quickly accepted by physicians, regulatory bodies, and reimbursement organizations, and it is faster, easier and cheaper to promote one drug across several indications than to promote an individual drug for each indication.

About the Author
David Twinberrow is senior director oncology, EMEA & Asia Pacific at IMS Health, with responsibility for guiding and developing the company’s global oncology franchise. He has in-depth knowledge of the commercial and clinical challenges of oncology gained from 14 years’ experience in the pharmaceutical industry, the last five of which focused specifically on the cancer area. He has also worked with a number of leading UK oncology centres in the development of an oncology prescribing system.