Despite advances in the prevention of some types of cancer, in the UK the lifetime risk of developing a malignancy remains in the order of one in three (Becker, et al, 1998). According to recent figures from CRUK (cancerresearchuk.org) nearly a quarter of all deaths in the UK are attributable to cancer, the four biggest killers being lung: 33,000; colorectal: 16,000; breast: 12,000; and prostate cancers: 10,000 (Office for National Statistics Mortality Statistics: Cause, 2004). With an ageing population and no sign of any significant reductions in the incidence of the major malignancies, the demand for cancer treatment is certain to increase in the future.

Given the scale of clinical need and the commercial potential for new cancer treatments, the high level of developmental activity in oncology is perhaps not surprising. At the same time, the pharmaceutical business environment is going through a period of significant change, with a slowdown in the number of new launches and an increasing shift in portfolio pipelines from primary care products to more specialist-driven therapies.

The oncology pipeline in particular is now the richest in number and potential of any therapeutic area with over 50 new chemical entities (NCEs) for cancer expected to enter the market over the next five years. This anticipated explosion of innovative anti-cancer therapeutics and technologies – including two new highly effective vaccines and a number of biologically led targeted therapies – is positioning the sector to

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Bridging the gap between approval and access in UK oncology practice

Oncology is fast becoming the most talked about area in UK medicine since the inception of the NHS in 1948. There are tremendous opportunities for companies entering this dynamic market but also significant challenges in securing usage in protocols of care. Vic Jhanjee and Philip Savage consider some of the issues

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be the number one therapy area by sales in 2010.

Against this promising outlook, there are already mounting cost pressures driven by the growing availability of treatment approaches with improved outcomes for a wide range of cancer types, changing patient demographics, and the need for a reconfiguration of cancer care delivery. As cancers increasingly become more chronic diseases, managing them over the rising survival time of the patients will be a growing financial challenge.

A UNIQUE AND COMPLICATED MARKET

It is important to recognise that oncology is not a single therapy area — there are several hundred different types of cancer, which sets the market apart from other therapeutic areas.

Breast, colorectal and non-small cell lung cancer (NSCLC) have the largest number of patients and as a result have attracted a high level of scientific, clinical and pharmaceutical research. These malignancies, because of their prevalence, have been the primary focus of research and development over the past 20 years, but in more recent times we have seen a growing trend towards the development, launch and marketing of treatment protocols for niche cancers, such as renal cell carcinoma. Although patient numbers are lower, high mortality and significant unmet need have made this an area of particular potential.

CLINICAL CHALLENGES

From a clinical perspective in the oncology setting, the challenges for new products entering the market are generally small. The fact that a new drug already has a licence confirms that it has passed an assessment process that on the whole would support its role in clinical practice. Frequently, many of the target clinicians will have been involved in clinical trials developing the new drug, or be aware of the results presented at major conferences prior to licensing. It would be unusual for a drug to have reached an audience that was not already familiar with its intended application. While there are individual oncology drugs that fail to capture the enthusiasm of the appropriate UK clinicians, almost invariably UK consultants are keen to prescribe new treatments in their area if clinical trials have demonstrated incremental benefits over existing protocols.

While there is no firm data to confirm this in the public domain, the pharmaceutical company's corporate identity and standing may have an impact on clinical trial participation and for use of a new drug in practice once approved by the National Institute for Health and Clinical Excellence (NICE). However, as we will see later, there are a number of important steps that drug companies can take to assist with drug usage locally prior to NICE review.

ECONOMIC CHALLENGES

From the payers' perspective, innovative new oncology therapies present issues around comparative value,
affordability and priorities – one of the biggest areas of concern for the health service is how to fund the increasing number of oncology molecules being launched onto the market. The UK is showing an increasing shift to more innovative treatments such as targeted therapies. However, due to their high cost these will cause further strain on already stretched healthcare budgets, likely worsen rationing and potentially rebound on pharma.

Pharmaceutical companies must therefore be able to show the true economic value of a drug – not only in terms of its direct cost but also the additional care that a patient requires during treatment, eg, infusions, nursing care, bed space, etc. Pharma companies are therefore increasingly being asked for health economics evaluations demonstrating the clear added value of their product in these terms. In reality, the true total cost of cancer care is very difficult to assess and this is undoubtedly a significant missing link in NICE deliberations.

Historically, the economic assessment of the costs associated with a new drug therapy has focused almost entirely on direct pharmacy costs – a figure used for most cost/benefit analyses. The NHS has a near monopoly of healthcare and expenditure in the UK and with the frequent calls for extra spending on expensive new drugs, not just for oncology but for other high-impact chronic illnesses such as multiple sclerosis and Alzheimer’s Disease, the UK government has chosen to keep decisions on the

“...increasing shift to more innovative treatments such as targeted therapies. Due to their high cost, these will cause further strain on already stretched healthcare budgets, worsen rationing and potentially rebound on pharma...”

Breast, CRC and NSCLC with highest patient numbers have attracted targeted therapies

Source: Oncology Analyzer MAT Q2 2006
balance of clinical benefits, economic costs and political pressure at arm's length via NICE, established in 1999.

Oncology drugs have been a key area of focus for NICE technology assessments, a process that involves wide formal consultation with key stakeholders including patient groups and interested pharmaceutical companies. While NICE considers a broad range of factors in making its appraisal, understanding the economic expectations of the therapy is central to its decision making.

Once a treatment has received a positive recommendation from NICE there is an expectation that it will become routinely available for those patients indicated. However, the funding arrangements for providing the product in question to these patients are not centrally supported. As a result, the adoption of a therapy supported by NICE may require Hospital Trusts and Primary Care Trusts (PCTs) to reduce expenditure in other fields of cancer care or indeed in other therapeutic areas since there is no discrete budget set aside for oncology drugs (Barrett et al, 2006).

**NHS Usage Prior to NICE Review or Following a Negative Appraisal**

As previously discussed, a NICE review is an essential requirement to achieving widespread NHS usage. However, there is generally an interval of 12-24 months from licensing a new drug until the release of the NICE appraisal, although in Scotland the similar Scottish Medicines Consortium (SMC) makes decisions more rapidly. During this time, there is potential for NHS patients to receive treatment with a new drug via two separate routes:

1. **Individual hospital use**
   Use by an individual hospital can be via a high-cost drugs budget, the objective of which is to allow limited prescribing of new agents prior to NICE approval. However, in most hospitals this requires an appraisal similar in its economic assessment to that undertaken by NICE or the SMC and, in our experience, is rarely successful if the figures are not in keeping with NICE guidelines.

2. **Individual patient use**
   An alternative is for the drug to be used on an individual patient basis by gaining permission from the appropriate PCT for each patient treated. By definition this is a time-consuming approach to individual patient care and is rarely successful. PCTs have internal assessment mechanisms to review high-cost drugs using the same format as NICE and the SMC and they are unlikely to reach differing views of the cost effectiveness of treatments without NICE recommendation. While there are isolated occasions where PCTs may support expenditure, routine experience suggests that this is unusual.

   Clearly these two methods require considerable input from the medical team and, increasingly, pharma marketing teams are providing materials and proformas to help with this time-intensive and mostly unrewarding approach to encouraging the regular use of new high-cost drugs.

**UK Private Sector Usage**

In the UK, an increasing percentage of the adult population holds private healthcare insurance – an appreciable market – with the majority of policies provided through employers rather than individual subscription. There is considerable variation in the numbers of patients with private cover around the country, with an obvious preponderance in the South East.

In contrast to the NHS system, the general policy of payers in the private sector is to support active treatment of malignancy that reflects accepted patterns of best practice. This therapeutic standpoint is virtually uniform across the private sector and, not surprisingly, one of the selling points of private healthcare is that it will guarantee access to the best and most up-to-date medical treatment.

In addition to use in the licensed setting, the private sector will also support some use of new drugs in unlicensed situations, as long as that use is supported by a sufficient base of expert publication/opinion.

**Deciphering the Oncology Market**

Operating in the oncology space is not the same as operating in the anti-allergy or ulcer-management area, for example, and companies pursuing opportunities there need to understand which model is right for them. Marketing to a specialist segment can be the most efficient as there is a smaller number of doctors and also a more focused set of the medical community which needs to be targeted. The marketing mix will therefore be vastly different from primary care and

“Oncology drugs have been a key area of focus for NICE technology assessments. While a broad range of factors are considered in making the therapy’s appraisal, the economic expectations are central to the final decision”
certain secondary care segments – eg, dermatology and urology – of the market where there is a greater emphasis on chronic, non-life threatening diseases.

The mainstay of promotion within the primary care sector revolves around seeing the right customers, the right number of times with the right messages. In the oncology sector there are other issues to consider, eg, the provision of robust clinical data, how to secure funding and identifying which treatment satisfies the stage of cancer.

In order to understand and address these issues, pharma companies must undertake a huge amount of primary and secondary research. They must then pick this information apart and piece it all together to formulate a coherent marketing strategy. Given the nature of this disease area and the complexities involved in terms of the tumour type, stage of cancer and whether combination or single therapy is being considered, making sense of the vast amounts of information can be a challenge to even the most seasoned brand managers.

Detailed analysis of patient-level data shows clear differentials in the number of patients across tumour types, stage of cancer and treatment stage. Having access to this type of information during the plan formulation process is therefore essential to a full understanding of the market.

**WHAT DO PRESCRIBERS NEED FROM THE INDUSTRY?**

Promoting an oncology brand is not the same as promoting one in the cardiovascular or allergy field. Nearly all consultants treating cancer in the UK are tumour site oncology specialists dealing with only two or three main tumour types. Even with the current expansion in oncology drugs, the actual number of new treatments for any individual tumour type is relatively small. Specialists involved in the treatment of cancer will almost certainly have been exposed to the vast array of clinical papers and studies published by pharmaceutical companies to demonstrate the efficacy of their drug and will be well informed about the latest developments. This begs the question, do oncologists really need additional clinical information or are they looking for something more from pharma to help them access a product for the patients they treat?

Given the increasing amount of paperwork that must be completed to justify funding for certain treatments on the market, the greatest gap for oncologists is support in developing formulary applications and business cases to secure product funding for individual patients. The vast majority – or at least their centres – would have been involved in the registration trials for any given product and they will therefore have a high level of familiarity and experience with the drug in question. They do not need convincing that it is going to be of benefit to their patients.

The government is now paying far more attention to the total cost of care as opposed to sole cost of the drug, when evaluating product prescribing. These additional costs include administration, nursing, bed space and other resource issues. Pharma companies therefore need to develop robust health economics arguments for their brand which take into account all of the variables associated with the drug. It is the overall cost of the drug that is likely to determine whether a product is going to be approved for reimbursement or not. The lack of budgetary resources to meet changing demand in this area calls for a much stronger focus on developing health technology assessment strategies that demonstrate real differential value and societal benefit.

**PATIENT CHOICE**

Given recent scientific advances and the increased focus on oncology, the pharmaceutical market is set for significant change for all stakeholders. Furthermore, many of these new treatments are likely to show no clear differentiation in terms of efficacy, safety and toxicity over existing products.

With the increase in competition, manufacturers will need to understand and monitor the impact of promotional efforts to a far greater extent than they have in the past. The increasing popularity of the Internet means that patients and doctors are in a better position to access information than ever before. In the UK, where there is heavy regulation on direct-to-consumer advertising, pharmaceutical companies nevertheless have the opportunity to provide valuable information on their websites. Oncology is an area where...
people are keen to learn more about medication and where knowledge in primary care is still sparse. In most other therapy areas, patients can obtain a great deal of information from their GPs, practice nurses or pharmacists. However, GPs are still not comfortable or sufficiently knowledgeable to talk about cancer care in any detail. Pharmaceutical companies should therefore ensure that their promotional efforts are not falling on deaf ears.

There are also increasingly frequent stories in the media regarding the funding of oncology products by trusts within the UK. Potential patients are therefore constantly exposed to information about products and have another channel through which to receive messages about why a drug should be used. Gone are the days when patients would listen to their specialist about treatment – many now come to specialists asking them about particular types of treatments.

**ISSUES IN APPROVAL AND ACCESS IN UK ONCOLOGY PRACTICE**

Manufacturers will need to take into account a number of issues long before a product is launched onto the market, including which indication to target first and the right point of entry, given that some indications will be shared with competitors sooner rather than later. Companies must also take into account how to differentiate their products to command and sustain a premium price.

One of the malignancies where two new targeted therapies have recently become available in the UK is renal cancer. This is an interesting example from both the perspective of the number of new drugs and also the expected – and unexpected – marketing challenges in developing their usage.

**Understanding the treatment paradigm is critical**

Breast cancer – chemotherapy  
Stage IV  
Proj. patients = 50,332

1st line 62.5%  
(Proj. patients = 31,458)

1. DOC 10.4%  
2. 5FU/CYC/EPI 9.4%  
3. CAPEC 6.8%  
4. DOC/EPI 6.5%  
5. DOC/TRAST 4.8%  
6. others 62%

2nd line 24.1%  
(Proj. patients = 10,765)

1. CAPEC 14.6%  
2. DOC 12.1%  
3. PAC 9.2%  
4. TRAST 9.6%  
5. VINOR 10.6%  
6. others 62%

3rd line + 9.6%  
(Proj. patients = 8,109)

1. CAPEC 13.1%  
2. VINOR 8.3%  
3. DOC 7.6%  
4. TRAST/VINOR 7.2%  
5. TRAST 4.7%  
6. others 59.1%

Source: Oncology Analyzer MAT Q2 2006
NEW DRUGS IN RENAL CANCER

Within the UK, there are around 6,800 cases and 3,600 deaths annually from renal cell carcinoma. Until recently, there has been little in the way of successful drug development in the area that has remained one of great unmet clinical need. Historically, advanced or metastatic renal cancer has been completely resistant to conventional chemotherapy drugs, with the mainstay of treatment being immunotherapy based on the use of interferon alone or combined with interleukin-2 and 5-fluorouracil.

Sorafenib (‘Nexavar’, Bayer) is an orally active, multikinase inhibitor that has broad spectrum activity against multiple tyrosine kinase pathways that are over-expressed in the malignant cell and contribute to its malignant growth. Compared with conventional chemotherapy agents, it has relatively modest toxicity with gastrointestinal upset and hand-foot skin syndrome being the most frequent issues. Sorafenib was licensed in 2006, with an orphan drug status, with the bulk of the supporting data coming from a trial presented at that point in abstract only. Sorafenib has been priced at £2,500 per month on the UK market, and was due to start its pathway to NICE appraisal in Feb 2007. To date, the NHS use of the drug has been minimal.

More recently, the full paper of the licensing trial has been published in the New England Journal of Medicine and review of the key points may well give an indication of how this drug will be viewed by NICE. The overall response rate was 10 per cent for sorafenib, compared to two per cent for the placebo, while median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group. Sorafenib has been examined by the SMC whose economic analyses based on the data presented in the original abstract gave these results: for good performance status patients the cost effectiveness was estimated at £27,689/QALY (Quality Adjusted Life Year) and for less fit patients £41,687/QALY. In light of these findings, the SMC’s recommendation was that sorafenib has not been demonstrated to be cost-effective and it would be surprising if NICE were to come to differing conclusions. Sunitinib (‘Sutent’ Pfizer) is a similar multi-targeted kinase inhibitor also licensed in 2006 for the treatment of renal cancer. Similarly to sorafenib it is yet to be appraised by NICE but has been reviewed by the SMC. The clinical and economic conclusions from the SMC were similar with the cost per QALY for sunitinib indicated at £39,000, which was deemed not to be cost effective.

The third new drug for renal cancer is temsirolimus (Torisel, Wyeth) – an inhibitor for the mTor kinase. This has been submitted to the FDA for licensing and is expected to gain approval in 2007. The trial data shows a positive comparison against interferon, with a similar expectation of benefit as seen with sorafenib or sunitinib, perhaps more so in poor prognosis patients, but Torisel has the problem of needing intravenous administration. To date, no economic or cost/benefit analyses have been performed on the drug.

ISSUES IN RENAL CANCER THERAPEUTICS

With no new drugs introduced since the 1980s, it would have been a step of profound optimism a few years ago to suggest that three new drugs for the treatment of advanced renal cancer would be introduced to the market within one 12-month period. This surprising state is likely to lead to a novel situation where new drugs sales and pricing will face competition from other new drugs, as opposed to being priced according to their inherent worth, or how much the market will bear. This competition between novel therapies will make for interesting decisions around usage and, as there is no current data on comparative efficacy, it may lead to the introduction of drug cost comparison as part of the clinical decision making process. More important, however, is the chosen benchmark for the NICE and SMC recommendation and the actions required of pharma companies to address this.

IMPACT OF DRUG ACTIVITY IN NON-RENAL CANCER MALIGNANCIES

The pathways targeted by sorafenib and sunitinib are not specific to just renal cancer and these drugs are likely to have activity in other forms of cancer. Recently, Onyx Pharmaceuticals which originally developed sorafenib announced very encouraging results from its use of sorafenib in hepatocellular carcinoma (HCC) with a significant increase in survival from treated patients compared with control patients treated with placebo. While this is a therapeutically welcome step, what makes it a very interesting situation for the economics.

“...This competition between novel therapies will make for interesting decisions around usage and, as there is no current data on comparative efficacy, it may lead to the introduction of drug cost comparison”
of renal cancer treatment is that hepatocellular carcinoma is a very common form of cancer (fifth most common worldwide) but occurs almost exclusively in patients outside the US and Europe.

In this situation, there will be a very large potential market compared to any other cancer drug market, but made up almost exclusively of patients and countries clearly unable to pay anywhere near the current drug cost of around £2,500 per month. The key issue will be the approach to this huge market and the impact the price setting for sorafenib in HCC will have on the price of sorafenib (grey/parallel imports) and so on the other treatments for RCC.

SUMMARY
The cancer drug treatment market is growing rapidly, due to the combination of increasing numbers of patients and now a significant number of new drugs. Some of these, of which rituximab is probably the best example, bring such a scale of benefit (10 per cent increased cure rate in high grade NHL for rituximab) and are marketed at such realistic prices that uptake becomes near-maximal within the first year or two after launch. In contrast, the benefits from most new drugs are likely to follow the more standard trend of drug development combining a modest increase in remission and survival with generally lower toxicity than the older treatments.

It is for these drugs that the pharmaceutical industry and governments/payers need to develop a plan to prevent the repeated scenes around UK hospitals in which patients are informed of or enquire about drugs which they have no reasonable chance of being prescribed in the NHS.

Historically, the UK NHS market has stood out as the one rich nation market that will not routinely pay for these drugs. But when one looks at the number of new cancer drugs coming to the market over the next five to 10 years, it is likely that this reluctance or inability to pay for non-curative courses of treatment that cost £30,000 or more will become an issue in the insured sector and also currently more generous state-funded system. The old model of launching a product in oncology and commanding a high price is no longer applicable. With the increase in products coming to market, there will be limited funding available for treatments.

We expect to see a period of considerable scientific and clinical advancement over the next decade, combined with a shake-up of the arrangements for paying for these new high-cost drugs. It is unlikely that the UK will change its ways. Instead, it is probable that other nations and major insurers will actually adjust their policies to exert an increasing degree of control over drug costs. It will be interesting to see how this developing problem is resolved.

To learn more about bridging the gap between approval and access in oncology practice, contact Vic Jhanjee at vjhanjee@uk.imshealth.com