Market and patient access to new oncology products in Europe: a current, multidisciplinary perspective


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To air challenging issues related to patient and market access to new anticancer agents, the Biotherapy Development Association—an international group focused on developing targeted cancer therapies using biological agents—convened a meeting on 29 November 2007 in Brussels, Belgium. The meeting provided a forum for representatives of pharmaceutical companies and academia to interact with European regulatory and postregulatory agencies. The goal was to increase all parties’ understanding of their counterparts’ roles in the development, licensure, and appraisal of new agents for cancer treatment, events guided by an understanding that cancer patients should have rapid and equitable access to life-prolonging treatments. Among the outcomes of the meeting were a greater understanding of the barriers facing drug developers in an evolving postregulatory world, clarity about what regulatory and postregulatory bodies expect to see in dossiers of new anticancer agents as they contemplate licensure and reimbursement, and several sets of recommendations to optimize patients’ access to innovative, safe, effective, and fairly priced cancer treatments.

Key words: cost effectiveness, drug approval, health-care access, health expenditures, innovative therapies, oncology

background

Health-care systems have had to become more sophisticated in recent years to accommodate an increasingly aged population, the development of myriad innovative technologies, new insights into disease processes, increasing demand for safe and effective treatments, and a greater interest in preventive medicine. In such an era it is not surprising that health-care expenditures, both in absolute terms and as a percentage of gross domestic product, are growing around the world. Even as the incidence of cancer is rising round the world, the cost of research and development for innovative pharmaceutical and biological products is increasing [1]. The trends towards greater patient demand and higher prices for anticancer medicines present significant challenges to both payers and the pharmaceutical industry as they strive to provide cancer patients with access to new, effective medicines. Licensure of new drugs requires that manufacturers provide evidence of their manufacturing quality, safety, and efficacy—the traditional three hurdles. Now, as health-care costs around the world spiral upward, reimbursement is often contingent upon evidence of cost effectiveness—the fourth hurdle [2]. In other words, sponsors must not only show that a drug is safe and effective but also they must demonstrate that it produces a health benefit sufficiently above that of available treatments to merit its additional cost [3], thereby ensuring that it will surmount the cost-effectiveness hurdle, achieve market access, and allow the sponsor to garner a return on its investment.

A number of concerns have been identified about the implementation of cost-effectiveness analysis (CEA), when it is used to decide which treatments a given health system will pay for. One concern is that the fourth hurdle may compromise patients’ access to innovative cancer drug therapies. There are also concerns that appraisals of cost effectiveness of new treatments are not always robust or transparent and that a lack of standardisation has led to variations in the cost-effectiveness

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thresholds both between and within health-care systems. In addition, stakeholders are concerned that postregulatory agencies take a restrictive view with regard to end points used to show the efficacy of novel agents.

To provide a forum for representatives of European regulatory and postregulatory bodies, pharmaceutical firms, and academia to candidly discuss and seek consensus on several critical points related to product licensure and appraisal of cost effectiveness, the Biotherapy Development Association (BDA) convened a 1-day workshop meeting in Brussels, Belgium, on 29 November 2007. The participants expressed support for the mutual goals of (i) delivering promising new agents to prolong the lives of cancer patients while maximising their quality of life and (ii) striving to optimally allocate resources among different health-producing technologies. This report highlights the discussion and outcomes of the meeting.

**the promise of innovative oncology agents**

No longer considered an acute, remitting disease that must be treated with combinations of cytotoxic therapy, surgery, radiotherapy, or some combination thereof, cancer is increasingly becoming a chronic, manageable disease, treatable with well-tolerated, chronic therapies directed against established molecular targets. Molecularly targeted therapy is guided by an understanding of relevant genetic variations among individuals with a particular disease and, when applicable, by the relevant molecular variations in the expression of that disease. This approach may offer the possibility of discriminating potential responders from nonresponders, identifying which patients are likely to benefit earlier in the disease pathway, ensuring appropriate dosing, reducing incidence of adverse events, and improving overall health gain [1].

Regardless, the sheer number and diversity of potential therapeutic targets and the wide spectrum of new anticancer agents are challenging pharmaceutical companies, regulators, and health-care providers to develop and evaluate regimens for treating individual patients. The essential needs of patients, however, remain unchanged: they continue to seek cure, relief of symptoms, and a longer, better life.

In particular, biologics, defined as substances isolated from a variety of natural sources—human, animal, or microorganism—and produced by biotechnology methods and other cutting-edge technologies [4], have shown great potential in cancer treatment, especially when used in combination with standard therapies (e.g. chemotherapy, radiotherapy) or with other biologics. Additionally, their use may spare patients from some of the toxic effects attributed to many conventional cytotoxic therapies.

The mAb rituximab (Rituxan™), for example, is frequently used in combination with chemotherapy or radioimmunotherapy for treating B-cell non-Hodgkin’s lymphoma. Results from a clinical trial included in the National Institute for Health and Clinical Excellence (NICE) appraisal of patients with stage II, III, or IV disease showed that 29% of those randomised to receive rituximab plus standard chemotherapy died within 2 years, compared with 41% of those given the standard regimen only [5, 6]. Another example is the mAb cetuximab (Erbitux™), which, when used in conjunction with standard platinum-based chemotherapy, improved overall survival (OS) of patients with metastatic squamous cell carcinoma (SCC) of the head and neck (median survival of 10.1 months) compared with cisplatin alone (median 7.4 months) [7]. These findings represent the first advance for treating late-stage SCC in quite some time and a significant milestone because therapeutic options for this group of patients are few. In another study, treating patients with irinotecan (Campto™)-refractory colorectal cancer with a combination of bevacizumab (Avastin™) and cetuximab (Erbitux™) led to favourable effects on overall response, time to tumour progression, and OS. Remarkably, patients who received a second course of irinotecan did even better, although they had been refractory to irinotecan before receiving the two biologic agents [8].

**the reimbursement hurdle**

The oncology market has grown considerably in recent years, driven by the advent of targeted therapy and the high level of unmet needs for effective treatment. The surge in new product introductions that began in 1997 has seen the size of the oncology market more than double in the past 5 years, with global sales reaching $35 billion in 2006. Much of this growth can be attributed to targeted therapies, which achieved sales of $13 billion in 2006, compared with $1.3 billion in 2001. Globally, the oncology class is now growing at 21% per annum—led by the United States at 23% and Europe at 22% [9].

Currently, oncology drugs account for 10%–20% of cancer-related health-care costs globally [10]. Payers, seeking ways to contain costs and allocate resources equitably, are requiring evidence of cost effectiveness of anticancer agents. Increasingly, pharmaceutical firms, too, are considering the pharacoeconomic picture to gauge the likelihood that their products will be able to surmount the fourth hurdle (demonstration of cost effectiveness).

Regulatory/licensing bodies and postregulatory/appraisal agencies often have slightly different goals (Table 1). The primary concern of regulatory bodies is safety and product efficacy, an estimate of effect under ideal circumstances, while the focus of postregulatory appraisal is clinical effectiveness, an estimate of effect in typical clinical practice and a typical patient population (the ‘real-life’ effect). Licensure of a drug does not guarantee patient access, however, because reimbursement authorities may judge that the cost of the therapy is greater than the health gain produced [11]. Gaining access to markets depends on the answers to two straightforward and legitimate questions posed by postregulatory agencies, such as the UK’s NICE or the Scottish Medicines Consortium (SMC): (i) How well does something work in comparison with what we already use (clinical effectiveness)? and (ii) How much health gain do we get for the money paid (cost effectiveness)? Sponsors should think broadly in order to get the right evidence at the point of launch. Then, when the evidence package is presented to the reimbursement authority, it is less likely that there will be problems obtaining access to market for the new drug.

**Regulatory/licensing bodies and postregulatory/appraisal agencies**

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<th>Regulatory/licensing bodies</th>
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<td>Focus on safety and product efficacy</td>
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<td>Evaluate under ideal circumstances</td>
<td>Evaluate in typical clinical practice and patient population</td>
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<td>Licensure does not guarantee access</td>
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Table 1. The gap between licensing (efficacy) and appraisal (effectiveness)

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We must bear in mind that payers want patients to enjoy health gains from increased survival and better quality of life. They also are concerned with equity of care, not just for cancer but other conditions as well. Payers, however, face certain pressures when it comes to oncology treatment. First, the number of oncology drugs being developed and licenced—especially targeted therapies—is on the rise. Secondly, as is the case with imatinib (Glivec™) for chronic myeloid leukaemia, treatment might be lifelong rather than a few cycles with a well-defined cost. Thirdly, with the increase in combination therapies, the costs are additive from a budgetary perspective, which increases budgetary uncertainty. Finally, there is a need to consider the service delivery environment (e.g. i.v. administration versus oral therapy). All these factors have to be considered in the context of overall budget impact and in terms of getting value for money and seeing that equity of care is achieved for all patients.

Pharmacoeconomics offers a set of tools to help decision makers better understand the value of treatment regimens. These methods provide a means of assessing the efficiency of treatments by systematically comparing the cost and consequences of treatment alternatives [12]. Several European Union (EU) countries use CEA, which compares the cost and consequences of two or more alternatives with a common therapeutic objective. In today’s health-care environment, a new treatment seldom displaces all other treatment options. Instead, postregulatory bodies must decide if the additional benefits offered by a new treatment justify its costs, compared with existing treatments. This decision is based upon an incremental analysis whereby the incremental change in costs of two treatments is compared with the incremental change in benefits of the treatments [12]. Incremental cost-effectiveness ratios (ICERs) quantify the cost per unit of benefit gained from using one treatment over another (often measured in quality-adjusted life years, QALYs) [13]. The method used for comparing cost and benefit varies from country to country, and different thresholds are relied upon by different health-care systems, reflecting differences in their health-care budgets and portfolios of health-care interventions provided.

Appraisals undertaken by NICE currently cover hundreds of technologies. Approximately 30% of published NICE appraisals involve cancer treatments. Of the 39 cancer appraisals undertaken up to June 2007, 35 recommended the use of the technology in some way and four did not. In most of the negative appraisals, the main reason for rejection was cost ineffectiveness (ICER > £30 000 per QALY). From Figure 1, it can be seen that there is a financial threshold ~£20 000 per QALY that factors into the decision to approve or reject coverage for a new drug. The threshold range employed by NICE is documented in its Guide to the Methods of Technology Appraisal although there remain areas of controversy and uncertainty [14].

A significant number of medicines recently reviewed by NICE are intended for difficult-to-treat cancers; this observation (combined with the apparent importance given to ICERs) may portend a difficult road ahead for expensive cancer therapies, which may be judged ineligible for reimbursement unless they provide correspondingly large health gains [15].

Other concerns about the utilisation of CEA in health-care resource allocation merit mention here. For example, incremental cost-effectiveness thresholds may not fully reflect opportunity costs; that is, choosing an intervention that increases QALYs but requires additional resources is an efficient use of those resources only if the additional QALYs generated exceed the opportunity cost in terms of the QALYs forgone from the interventions that will need to be cancelled to free up enough resources to support the new intervention [13]. The appropriate threshold for a positive decision is a function of the efficiency of the activities that will be displaced to fund the new intervention, which is, in turn, a function of the budget impact of the new technology and any changes in the total budget. The use of a single static threshold is not consistent with these factors unless the additional cost of positive decision is met by an increase in the budget. In addition, static thresholds do not allow for periodic adjustments for changing economic circumstances and societal priorities. It must be borne in mind that CEA per se is not designed to contain costs; it is designed to inform the optimisation of health outcomes from a given budget [16].

Despite these challenges to CEA, it is likely that decisions on pricing and reimbursement will continue to be based, at least in part, on evidence of cost effectiveness. It is incumbent, therefore, on pharmaceutical companies to ensure that the hurdles of both clinical effectiveness and cost effectiveness can be cleared by products in development. Sponsors must ensure that the necessary studies are undertaken as part of drug development in order to generate the required data [15], and
postregulatory bodies must apply robust tools for economic evaluation in a transparent decision-making framework.

**Reducing the Element of Risk in Drug Development**

To ensure a return on their investments, sponsors need to reduce the risk of failure during the pivotal clinical trials (phase III) of innovative anticancer agents. And yet, regulators are often asked to license anticancer compounds based on less-than-convincing evidence from single-arm trials, single pivotal trials, intermediate end points (e.g. response rate, progression-free survival), unvalidated biomarkers, results of interim analyses, placebo-controlled trials, and cross-over trials. To address such concerns, the BDA delegates spoke at some length about topics related to the design of clinical trials. These discussions are summarised below.

**Translational Science**

One important reason why investigational anticancer biologics fail in phase III of the drug licensure process is insufficient understanding of their mechanisms of action [17]. To reduce the risk of failure, it is necessary to understand the biology and medicine of tumours through translational research. Rational drug development should be based on the knowledge of mechanism, often elucidated with ‘-omics’ studies (e.g. genomics, metabolomics, proteomics). Negative proof of mechanism (POM) should be a clear no-go signal, and a positive POM or proof of concept can streamline subsequent development by ensuring that studies are testing the drug-target hypothesis.

To maximise their chances of success, sponsors must anchor their drug development programmes in rigorous translational science:

1. Unlock innovation in the clinic: conduct broader screening of possible indications, adopt the mind-set of an inventor rather than a tester, and establish strong team structures.
2. Conduct rapid ‘safe efficacy’ screening: plan for earlier patient trials of agents that appear to be safe, keeping in mind that studies in mouse models are unlikely to be predictive for humans. Apply real-time data tracking to allow earlier and more frequent review of the go/no-go decision.
3. Focus on realistic commercial strategies, especially those based on validated biomarkers: dose-ranging and adaptive-trial designs are important, and it is critical to ensure that phase II end points are consistent with those for the subsequent phase III trial.
4. Design winners: develop a differential strategy and think hard about cost effectiveness in addition to effect size and the potential market size.

**Biology-Driven Clinical Development**

Historically, drug development has emphasised clinical considerations, with scant attention paid to research on the biological underpinnings of the agents in question. To reduce the risk of failure, we must understand the biology and medicine of tumours through translational research. The objective of early-phase (I/II) studies should be to confirm the agent’s pharmacology at a safe dose while elucidating the underlying physiology and hypothesising how the drug or drug combination could influence the course of disease. The more that is learned in the early phases, the greater the chances that the subsequent confirmatory (II/III) study will be successful [18]. Such an adaptive learn-and-confirm approach, as advocated by Lewis Sheiner [19], in which pharmacostatistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers a quantitative approach to improving drug development and development decision making [20].

This approach could promote greater understanding of an agent’s medical and commercial value as well as its safety. Transition times (between phases) should be shorter because of greater efficiencies (Figure 2), and nearly seamless phase I/II and II/III designs would allow real-time flexibility.

**End Points**

Current regulatory end points were developed over the course of the past 30 or 40 years for evaluating cytotoxic chemotherapies. The gold standard for end points in oncology studies remains OS, which is a tangible and straightforward measure used for assessing benefit and risk. Under certain conditions, however, sponsors may use other end points, for example, if life expectancy or the study’s duration is long, if alternative treatments are available, or if the sponsor is not making a claim of improved survival.

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**Figure 2.** Proposed paradigm for drug development based on Sheiner’s principles of learn and confirm [19].
Regardless, conventional oncology end points may not always be appropriate for judging the efficacy of new anticancer biologics [21]. In unselected patient populations, it would be difficult if not impossible to show beneficial effects by relying solely on OS. Surrogates, such as disease progression end points, can sometimes be used for evaluating targeted biologics. Sponsors must bear in mind, however, that regulators are cautious about licencing drugs based on surrogate parameters unless those measures are plausible and validated. There are several examples from other fields of medicine in which the use of surrogate response led to erroneous conclusions about safety or efficacy. In oncology, objective response rate (e.g. tumour shrinkage), in some trials, has appeared very promising but was not reflected in increased OS. Furthermore, reimbursement authorities need to understand the relationship between the surrogate and health gain in order to be confident about the magnitude of the treatment’s impact on health. These findings support the view that the design of pivotal trials remains critical. The questionable value of some surrogate end points currently used could potentially reduce their usefulness to regulatory and postregulatory authorities charged with evaluating and approving therapies for reimbursement.

Traditional clinical trials generally are designed to evaluate one agent at a time. Because targeted therapies are frequently used in combination or sequential treatments, attributing survival benefit to a specific therapy requires careful study design and analysis or the results may be uninterpretable or meaningless [22, 23]. Alternative combination therapies can be compared in a trial to provide evidence that the difference in outcomes is attributable to the different content of the combinations, provided that only one component differs or that the intent is to obtain a licence for the combination treatment. Sequential therapy trials are more challenging. It is thus critical that end points used in evaluating an intervention be specific to that intervention and reflective of a biological effect on the tumour while capturing its impact on health.

A tension arises, however, because regulators demand evidence to support the use of biological outcome measures as end points for clinical evaluation and payers need to see a link to health. The more robust the link between biological outcomes and health, the more satisfied payers will be. Without a strong evidence base for the health benefits from the new treatments, health-care decision makers will be reluctant to approve new therapies for reimbursement. Industry and regulators, therefore, need agreed-upon end points for pivotal trials in oncology. In the current environment, where regulators are responsible for consumer protection, the onus is on industry to ensure that oncology pivotal trials use end points that meet the evidence needs of reimbursement authorities. Possible adjuncts to the gold standard OS end point are (i) clinical end points that may indicate longer life and/or improved life [e.g. progression-free survival, time to progression, quality-adjusted time without symptoms or toxicity (QTWIST)]; (ii) surrogate end points (e.g. response rate, duration of response) that consistently predict for the clinical end point and are predictive of health gain; (ii) validated biomarkers that are indicators of a biological effect of the intervention; (iv) surrogate markers (e.g. CA125, carcinoembryonic antigen, results of positron emission tomography imaging) that predict a clinical end point; and (v) functional imaging technologies, such as combined positron emission tomography/computed tomography [24], which can be used to measure early treatment response as well as drug distribution within the body. Such alternatives, especially if applied in combination with OS data in a pivotal study, are likely to support the outcome of licensure and may be of value to postregulatory agencies, too.

Patients frequently experience toxic effects as a consequence of cancer treatment, but only a small proportion experience clinical benefit. Therefore, in addition to clinical or surrogate end points, patients’ health-related quality of life (HRQoL) plays an increasingly important part in drug registration and is frequently an essential part of the evidence base for reimbursement decisions [14]. Measurement of HRQoL attempts to investigate the direct effect of a medical intervention or a therapy on a person’s ability to function well in his or her daily life. Quantity of life is measured in terms of life expectancy. Economic evaluations frequently attach a value to HRQoL via utility measurements. These utilities are combined with life expectancy data in the calculation of QALYs [25]. In the area of oncology treatments, which may entail negative side-effects, including HRQoL data that capture the impact of the negative side-effects as well as the longer-term benefits of treatment in a drug’s dossier might tip the scales in favour of registration or reimbursement. In the extreme, the absence of such data can represent an insurmountable barrier to a positive recommendation; for example the SMC is unable to recommend for use products if companies have failed to submit economic evaluation dossiers.

HRQoL data are valuable for postregulatory appraisals because they are the means by which clinical end points can be translated into health outcomes. QALYs are increasingly being considered in postregulatory approval decisions by bodies such as NICE and SMC, and truly positive, clinically relevant improvements in HRQoL could serve as a basis for recommendation and approval. Many validated HRQoL instruments are available, but most are designed to measure general HRQoL. The sensitivity of these instruments to the impact of cancer and cancer therapies on HRQoL has not been established. In addition, the longitudinal performance of existing HRQoL scales in the cancer patients warrants further research, including assessing the need for new instruments [26]. The lack of HRQoL instruments validated for use in cancer patients represents a significant constraint on the capacity to demonstrate the value of innovative anticancer treatments.

The relative value of currently used HRQoL instruments remains somewhat contentious. While reimbursement agencies are interested in the information they attempt to capture, the ability of current measures to adequately capture real improvements in health is often questioned. Improvement in the design and application of HRQoL data would be of value to regulatory and postregulatory agencies and all stakeholders.

**patient selection**

Pharmaceutical companies recognise the need of budget holders to receive value for money. Responding to this need is part of the rationale for developing biomarkers and pharmacogenetic approaches to identify population subgroups...
that will receive maximum clinical benefit while at the same
time minimising adverse events among those less likely to
benefit from a given treatment.

The use of patient selection is perceived to be critical when it
comes to conducting clinical trials of new biologic anticancer
agents, which are increasingly based on molecular profiling and
more detailed classifications of malignancy [27]. One can
envision three possible outcomes of the subgroup analysis in
trials of such agents: (i) the optimal situation, in which the
subgroups were prospectively defined and adjusted for
multiple-testing bias; (ii) in an overall positive study, the
exclusion of nonresponding (resistant) subgroups from post hoc
analysis, so that such a study probably has a good chance for
regulatory approval; and (iii) positive results based on analysis
of subgroups identified post hoc even though the study overall
had negative or nonsignificant results. The subgroup results in
such a case might be useful for generating hypotheses but
probably could not serve as a basis for approval. Nevertheless,
reimbursement authorities are not so constrained in their use
of subgroups as the licensing bodies. Often reimbursement may
be approved for post hoc subgroups provided that there is
a biologically plausible basis for the differential effectiveness/
cost effectiveness and that the defining characteristic of the
subgroup can be defined before the treatment choice is
made. Nevertheless, because post hoc subgroup analysis may
introduce bias into the overall summary effect, it should
certainly be avoided in pivotal studies.

When faced with a dossier based on subgroup analysis,
regulatory agencies must consider several important factors
that could affect how the results are interpreted and the
findings used in patient treatment [14, 28, 29]. For example, if
a pivotal study using a suboptimal dose showed suboptimal
efficacy, it would not necessarily warrant a negative assessment.
So long as the difference between the treatment groups is
significant, approval may not be affected. Regulators must
also ascertain the reliability of the methods used for patient
selection (e.g. -omics, genetic testing, immunohistologic
techniques). Subgroups will never be perfect; frequently there
may be some overlap between responders and nonresponders.
Reimbursement authorities are concerned not only with the
performance characteristics of the identification technique but
also with the feasibility of implementing it in a service setting.

Very strong preclinical and theoretical evidence exists that
targeted anticancer agents should work, but is the
pharmaceutical industry interested in pursuing the
development of targeted oncology drugs if only a segment of
the patient population is likely to benefit considering that the
price of developing a new drug may run close to $870 million
[30]! In general, selected patient populations can work on
a commercial basis. From a marketing perspective, it is
always prudent to focus on the best audience, regardless of the
nature of the product. Even in the setting of very rare tumours,
manufacturers can capitalise on rational drug design for
markets of high unmet need and a low bar for surpassing the
efficacy of available therapies and thereby achieve commercial
success [31]. It is possible, however, that some active therapies
(e.g. matrix metalloproteinase inhibitors) have already been
discarded because of a lack of methodologies to detect activity
in small subgroups in unselected populations. We need new
approaches if we are to fully exploit the opportunities that a
greater understanding of the biology would provide.

orphan drug status

Manufacturers and payers alike must bear in mind that, in this
era of personalised medicine in which some treatments are
tailored for subgroups of patients based on biomarker expression
or other biologic or genetic factors, a majority of innovative
anticancer drugs could be considered orphan drugs. According
to EU Regulation 141/2000, orphan drugs treat life-threatening
or chronically debilitating conditions with a prevalence of
fewer than five cases per 10 000 population [~250 000
patients in the European Economic Area (EEA)] for which no
satisfactory alternative approved treatment exists or the new
drug could bring significant therapeutic benefits.

Although each rare disease affects a small number of
people, collectively they will affect up to 6% of the EEA
population at some point in life, meaning that some 30 million
Europeans are affected or will be affected by a rare disease.
All cancers, except for the five major tumour types [breast
(female), lung, colorectal, prostate, and bladder], are rare
diseases, according to this classification [32].

Pricing of orphan drugs has sometimes seemed to be an
arbitrary matter because of guarantees of market exclusivity,
lack of alternative treatments to offer patients, and scant
information on medical benefit at the time a price is sought
[32]. Nevertheless, the cost of orphan drugs has generally been
one society was prepared to pay because such treatments
were so uncommonly available that their budgetary effect was
negligible. Nevertheless, there has been a significant increase
in development of orphan drugs in response to efforts to
address the significant unmet clinical needs of people affected
by rare diseases. Consequently, payers now anticipate
increasing costs as more orphan drugs reach the market [32].
In response, payers have begun exploring when they should
be willing to pay more for orphan drugs and how much [33].
It is unlikely that future innovative oncology products will
be completely excused consideration by reimbursement
hurdles because of their orphan status [34–36].

postmarketing studies

Oncology is an area in which there is much to be done even
after a drug is approved. The common goal of pharmaceutical
firms and regulators is to get effective drugs to patients as
soon as possible. Jonsson and Wilking [10] recently
recommended reducing the time for authorising the marketing
of new therapies, expediting the availability of therapy at
a national level by streamlining negotiations on pricing and
reimbursement, conducting economic evaluations and health
technology appraisals rapidly and aligning them with market
access, and undertaking more effective budget planning by
payers to accommodate new therapies. Nevertheless, rapid
implementation does pose important challenges. The
availability of a therapy in routine practice makes it difficult to
undertake the research necessary to provide reassurance that
the new treatment is, in fact, a cost-effective use of resources.
In this setting, the benefits of the agent may be uncertain, but
the opportunity cost—resulting from health-producing
activities or treatments that must be forgone to pay for the new treatment—is not.

Reimbursement authorities need to balance the expected health gain from expedited implementation against the cost of the implementation and the risk that further evidence will demonstrate that the treatment is not a cost-effective use of resources. They will also wish to structure the implementation process to ensure that it is capable of providing robust evidence of cost effectiveness to inform subsequent reviews [37].

Better-controlled postmarketing studies may help determine whether new drugs will meet their effectiveness and cost-effectiveness goals. Some will fall short, but others might be better than anticipated. One possibility would be to have a period when a new drug is available under controlled conditions to generate more data, after which the price would be re-established [38]. For such an approach to be attractive to the developers of innovative treatments, it would be important that drugs that prove to be more effective than anticipated could command higher prices after the new effectiveness data were reviewed.

**some innovative proposals to increase access**

All purchasing decisions are tied to some degree of uncertainty and risk. In the case of new health-care technologies, these concerns are typically manifested as uncertainty regarding the external validity of clinical trials data, a lack of clarity about interim results and surrogate end points, uncertainty surrounding long-term clinical effectiveness and cost effectiveness, and issues of safety in widespread usage. Substantial uncertainty will often persist even after reimbursement approval. Currently, payers bear the risk associated with most purchasing decisions. If a product does not live up to expectations, the payer has wasted scarce health-care resources, and there is currently no means for financial redress from the manufacturer. Payers do, however, have a degree of power they can exercise in their purchasing decisions. Consequently, novel approaches, such as conditional reimbursement (conditional coverage) and risk sharing, are being developed by payers to redistribute the risk between them and the drug suppliers.

**conditional reimbursement**

In the case of conditional reimbursement, payment for a drug may be contingent upon meeting specific criteria or adhering to certain rules. For example, the application may be restricted to specific categories of patients or prescriptions may only be provided by authorised physicians [39]. During the postmarketing period, the producer generally is required to continue to develop evidence on the clinical effectiveness and cost effectiveness of the drug. Along these lines, the US Center for Medicare and Medicaid Services has implemented a conditional coverage scheme known as coverage with evidence development [40], which places conditions on the continued coverage of new technologies [41]. Such approaches to reimbursement are currently being considered for implementation in several EU countries.

**risk sharing**

A risk-sharing arrangement is a specific form of conditional coverage that entails a contractual agreement between a payer and a health-care supplier or manufacturer [42]. Typically, such arrangements are based on a ‘guaranteed’ outcome resulting from the treatment [43]. A range of outcomes can be specified in risk sharing: a clinical end point or a humanistic/HrQoL outcome, resource outcome (effect on use of health-care resources), financial outcome (effect on health-care budget), or even an economic outcome based on a cost-effectiveness threshold. To date, technologies that have been covered under such arrangements have tended to be for severe indications with great unmet need, substantial uncertainty about effectiveness (promising but not yet significant trial results), high cost/budgetary impact, or a strong political/patient lobby demanding access. In several EU countries, reimbursement authorities are increasingly looking at such innovative strategies as a means of providing selective patients with access to new therapies and, at the same time, managing some of the risk associated with providing expensive drugs that do not always work.

Since 2006, the National Health Service of Italy [Servizio Sanitario Nazionale (SSN)] has been using risk sharing as a means of expanding patient access to new anticancer drugs, which are often very expensive but only sometimes effective. For example, erlotinib (Tarceva™), as second- or third-line treatment for advanced non-small-cell lung cancer, is paid for at half the usual price for the first 2 months for all patients, thereby refunding the cost for the proportion (~50%) of patients who would be expected to have disease progression at or before 8 weeks of treatment, according to the results of the pivotal trial. Similar programmes have been set up for sunitinib (Sutent™) and sorafenib (Nexavar™) in advanced kidney cancer: the agreements stipulate that half of the first 3 months’ treatment is provided at no cost by the manufacturers, with response assessment planned after 12 weeks. Dasatinib (Sprycel™), for treatment of leukaemia, is reimbursed under a similar risk-sharing agreement. In all cases, when treatment is continued after response assessment, it is reimbursed at full price. In the short term, this system has allowed the SSN to provide patient access to oncology agents while giving opportunities to drug manufacturers to earn a return on investment when their products work well and for a long period [44].

A similar risk-sharing arrangement was used in UK as a basis for providing bortezomib (Velcade™) for treating multiple myeloma. This innovative programme ensures that the National Health Service pays for the drug only when patients show a full or partial response to treatment (50% reduction in serum M-protein concentration) after four cycles of treatment [45]. If the patient does not respond sufficiently, the manufacturer must rebate the full cost of bortezomib treatment [46] or provide replacement product.

Such arrangements provide patients with access to the drug while potentially minimising the risk of wasting scarce health-care resources. The effectiveness of such risk-sharing schemes in reducing the risk of wasting health-care resources depends upon the measurement properties of the assay, the strength of...
the relationship between the assay and actual health gain, and the ability of the service to monitor outcomes and the resource intensity of the risk-sharing infrastructure. To date, there has not been an effective evaluation of these risk-sharing schemes in terms of their effectiveness in promoting access to innovative new products or their effectiveness in promoting efficient use of limited health-care resources.

In general, risk-sharing agreements should be the exception rather than the rule because they are expensive to implement and monitor, and they introduce additional uncertainty for manufacturers about their future income stream, and they move a significant portion of the experimental phase of product development process from before to after the licensure hurdle. Risk sharing is most likely to succeed if an indication has few available treatment options or if there is significant patient pressure for access. In designing such schemes, attention should be paid to ensure that they do not become costly and bureaucratic processes that are burdensome to health-care professionals and the health-care system as a whole. Such arrangements can pose significant financial risks for manufacturers as well as the payers and should not be viewed as a shortcut to overcome barriers to market access. Some have suggested that uncertainty could be better resolved through further clinical research [47].

**manufacturing efficiencies**

Unlike conventional small molecule therapies, cost of drug production represents a substantial determinant of the total cost of biologic products. The manufacture of biologics occurs in a small number of very costly, large, single-product incubators. With these agents, substantial and very risky investment is necessary before a phase III trial programme can commence so that there is sufficient production capacity available. A bioincubator, which is typically dedicated to generating a single biologic, can cost >$1 billion [48], financed by venture capitalists expecting a 20% annual return on capital [49]. Assuming that the manufacturing investment is made 2 years before licencing, a pharmaceutical firm would have to incur debt exceeding $1.4 billion for manufacturing alone before the product is launched.

To date, actions to reduce production costs do not appear to have been considered as part of the solution to the high cost of innovative new therapies. If production costs could be lowered,
so could drug prices. For example, could a distributed production network based around disposable technologies reduce the costs of production? The UK has >220 bioincubators, representing a substantial infrastructure. Using a distributed production network model might shift the manufacturing investment closer to the time of—or even after—licensure of the biologic. Innovating companies could outsource production after reimbursement is approved or licence the cell line to local manufacturers. The result could be significantly decreased production time and reduced investment costs. This, in turn, could feed into lower prices for innovative therapies, making them accessible to a greater proportion of the patients who could benefit from them.

Such an approach would require an entirely new way of thinking. The barriers to the development of this type of alternative approach to the manufacture of biologics are significant. With biologics, it is frequently stated that the product is the process; therefore, establishing that production processes were operationally equivalent would be essential. However, the cost of these validation processes would have to be carefully managed if they were not to outweigh the efficiency savings. Current regulatory frameworks would have to be modified if the potential efficiencies are to be realised. The effective implementation of this production model would require a skilled bioengineering workforce on a scale that does not currently exist.

Innovative productive technologies may be part of the solution to the high cost of new biologic therapies; but this would depend upon system-wide changes. However, given the scale of the health benefits available from making innovative products more widely available, change on this scale may be justified.

**recommendations**

The BDA delegates formulated recommendations targeted at every level of the clinical research enterprise, with the aim of improving the access of patients to novel anticancer drugs and the access of sponsors to markets for those drugs. The recommendations are presented in Table 2.

**conclusions**

Targeted anticancer treatments are on the basis of a well-founded concept and are likely to be the basis for sustaining and growing the pharmaceutical industry in the years to come. Across Europe, health-care payers are confronted by the challenges of resource scarcity in the face of infinite demands. Despite budgetary constraints, there is tremendous political pressure to have new drugs licenced and made available to patients. Postregulatory agencies must take into account opportunity cost, morbidity, and the marginal benefits associated with new therapies to discern which drugs truly make a difference—the ‘real winners’. For their part, pharmaceutical firms should embrace a new learn-and-confirm paradigm for drug development on the basis of translational science and feedback from postclinical study, which may lead to rational selection of patients, identification of new areas for basic research, and earlier recognition of agents most likely to surmount the fourth hurdle of cost effectiveness.

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