ELSEVIER

Health economics and outcomes research within drug development
Challenges and opportunities for reimbursement and market access within biopharma research

Floortje van Nooten[1], Stefan Holmstrom[5], Julia Green[3], Ingela Wiklund[1], Isaac A.O. Odeyemi[2] and Teresa K. Wilcox[4]

[1] United BioSource Corporation, Hammersmith, London, UK
[2] Astellas Pharma Europe Ltd, Staines, UK
[3] United BioSource Corporation, Lexington, MA, USA
[4] United BioSource Corporation, Bethesda, MD, USA
[5] Astellas Pharma Global Development, Leiderdorp, The Netherlands

Healthcare decision makers who determine funding for new medical technologies depend on manufacturers to provide evidence of the technology's efficacy, safety and cost-effectiveness. Constrained budgets and increasing reliance on formal health technology assessment (HTA) have created an abundance of external hurdles that manufacturers must navigate to ensure successful product commercialization. These demands have pushed pharmaceutical companies to adjust their internal structures to coordinate generation of appropriate evidence. In this article we summarize internal and external opportunities for manufacturers to establish a foundation of evidence for successful market access, starting in Phase I of development and continuing throughout the post-approval product lifecycle.

The goal of any healthcare intervention is to improve health. Preventive measures, non-pharmacological and pharmacological treatments, and medical procedures are among the numerous technologies available to better health. Healthcare decision makers need to make decisions about which technologies to adopt based upon the patients' needs and the safety, efficacy, effectiveness, budget impact, cost-effectiveness of the technology as compared with existing treatment options. Decision making in healthcare is a complex process taking place along a continuum that starts with evidence generation followed by deliberation on each particular intervention and then communication of the resulting decision to key stakeholders [1]. To successfully complete this process, decision makers require considerable evidence at each step along the development continuum. In recent years, the emphasis on evidence has become even more essential, because governments confronted with dwindling budgets strive to curtail costs. The economic downturn has placed increased pressure on manufacturers to be cost-conscious by streamlining their drug development program in addition to their commercialization processes.

Before product launch, healthcare decision makers depend on manufacturers to generate evidence for new interventions. Lack of appropriate evidence to quantify the efficacy and safety of novel compounds and limitations in accessibility (i.e. lack of published or accessible data) and usability (i.e. applicability of evidence supplied by biopharma or academia to policymaking) of evidence have been identified as barriers for informed healthcare decision making [2]. These barriers are a reminder that those who provide the health-based information and those who use it approach the decision-making process with different perspectives [2] and with different goals. Even with an adequate quality or quantity of evidence, the data still needs to be evaluated and judged by heath policymakers [3] to justify the added value compared with existing therapies in the market. Tunis postulates that disagreements in healthcare decision making are more often a consequence of differences in opinion among key stakeholders about the role of evidence than a consequence of differences in judgment of health policy [4].

The importance of providing appropriate evidence for supporting healthcare interventions' adoption globally is demonstrated

Corresponding author:. van Nooten, F. (floortje.vannooten@unitedbiosource.com)

1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2012.01.021

by recent examples of products failing to gain approval for coverage or reimbursement from national reimbursement and/or health technology agencies. Neumann *et al.* found that technologies with strong evidence bases were more likely to be covered by Medicare (USA indigent health coverage) than those with fair or poor evidence bases [5]. As examples, the Australian technology appraisal group (Pharmaceutical Benefits Advisory Committee) rejected a cholesterol-lowering drug for patients with type II diabetes owing to an inappropriate choice of comparator within its clinical trial [6]; the Scottish authority (Scottish Medicines Consortium) rejected an osteoarthritis drug because the manufacturer did not provide a sufficiently robust economic analysis [7]; and Canadian authorities (Canadian Agency for Drugs and Technologies in Health) rejected a venous thromboembolism prophylaxis drug because they considered the trial data insufficient compared with the currently used standard of care [8]. With technology appraisals having such an important role in decision making for adoption of an intervention and making or breaking market access, pharmaceutical companies need to plan for the assessment evidence desired by reimbursement-focused decision makers throughout the clinical development of their product [9].

Achieving market access for a new product involves understanding the current evidence requirements for reimbursement, recognizing the challenges these hurdles pose for drug developers and identifying tactics to address these challenges. In this article we summarize the role of health economics and outcomes research (HEOR) in providing a foundation for evidence for successful market access and reimbursement for pharmaceutical products across several key markets, spanning the entire drug development lifecycle, from early proof-of-concept studies through product launch to post-approval product cycle management.

Current evidence requirements for reimbursement

Achieving market access for a new product typically involves several steps. Approval by a regulatory body to obtain marketing status is based on the efficacy of the product [clinical outcomes and patient-reported outcomes (PROs)] and safety; PRO data can include symptoms, physical functioning, or health-related quality of life (HRQoL). If a product is to be funded or reimbursed by payers, additional conditions need to be fulfilled prior before market launch. Criteria for access vary across countries but can include unmet medical needs, the effectiveness and safety of the drug, drug price, budget impact and cost-effectiveness. In addition, the product might be assessed at a national, sub-national or regional, or, in the case of the USA, at individual payer levels. HTAs conducted by national agencies are likely to influence the pricing accepted within a country or by a specific regional payer. For pricing in most countries, the manufacturers must negotiate with the appropriate agency to agree upon the product price. Agencies involved in price negotiations are likely to either have conducted the HTA or to have received an assessment conducted by a sister agency within the country.

Reliance upon HTAs has been growing over the past years, and most European, Asian, North American and Australian healthcare payers require some level of product assessment after marketing authorization to assess new benefits of intervention. The type of information required during the reimbursement process differs by country and can generally be divided into two groups: countries mandating only clinical data and countries mandating both clinical and cost-effectiveness (economic) data. In general, payers would like to see 'value for money' or value-based pricing and avoid paying for products that do not provide any additional benefit over current treatment options. Justifying the value of a product is increasingly important for gaining reimbursement. 'Value for money' refers to the value of the product for the patient; it provides good efficacy at a reasonable and competitive price [10]. Payers are also increasingly focusing on products that can be seen as 'innovative'. Definitions of 'innovation' vary across stakeholders, but it can generally be defined as improvement in relative efficacy and/or efficiency compared with the current standard of care. A 'valuable innovation' is defined as something that truly fills an unmet need [11].

External challenges in providing the evidence for successful product commercialization

Well-established factors for achieving successful product commercialization include preparing the market (engaging key opinion leaders, establishing treatment pathways and guidelines), mobilizing sales and marketing teams, and engaging with formulary authorities. With the growing requirements for reimbursement from healthcare decision markers, generation of HEOR evidence has become an increasingly relevant aspect for obtaining market access. Because different markets (countries and health authorities) have varying requirements for health technology appraisals, it is challenging to anticipate and meet all of the information needs. All markets require licensing approval before reimbursement consideration, but reimbursement assessment might be required before market access in some settings (e.g. in France, Australia and Sweden). Assessment most often requires the development of product-specific dossiers for which the evidence requirements differ substantially from those used in a licensing submission, even if they are based on the same data generated throughout the clinical development process. Table 1 provides a summary of evidence types considered or required for assessment by selected countries.

Given that the evidentiary requirements for successful reimbursement are real and substantial and vary across markets, one of the largest challenges that pharmaceutical companies face in the development process is identifying and reconciling differences between licensing requirements and reimbursement requirements. These differences must be understood, openly discussed and jointly prioritized among internal stakeholders for a product to gain optimal market access (Table 2).

Demonstrating effectiveness in addition to efficacy

Licensing agencies are interested in the benefit–risk assessment of a product within a rigorously controlled setting where internal validity is paramount. Sound clinical trial data (evidence of efficacy and safety) have always served as the cornerstone for regulatory approval, and until recently, efficacy and safety were often all that was (and in some cases still is) required for access to the market and reimbursement. Randomized controlled trials (RCTs) are (and must remain) a crucial step in product development. However, reimbursement authorities are more interested in the relative effectiveness of a product compared to the local standard of care. Before launch, medical products are tested in controlled

TABLE 1

Important parameters in the reimbursement process in individual countries [30]

	Australia	Netherlands	Canada	France	Germany	Sweden	Italy	UK
Clinical effectiveness	✓	✓	✓	✓	✓	✓	✓	✓
Cost-effectiveness	✓	✓	✓	✓ (post-launch)	✓ (only in specific cases)	✓	✓	✓
Innovation[a]				✓			✓	

Note: Please note that this table was up-to-date at the time of submitting, however, things keep evolving within healthcare systems, which means this table might change over time.
[a] The term 'innovation' lacks specificity and differs by country. Only Italy has published criteria for identifying an innovative product [31]. With this algorithm, pharmaceuticals are designated as an important, moderate, or modest therapeutic innovation based on (i) the availability of existing products or (ii) the extent of the therapeutic benefit. In France, an improvement of medical benefit (ASMR) level (major innovation, important improvement, significant improvement, minor improvement and no improvement) is assigned for each product, but the criteria used to determine these levels is not defined by the Haute Autorité de Santé. Despite the potential for unclear or conflicting definitions of innovation, the value of demonstrating innovation remains high for reimbursement authorities.

TABLE 2

Distinctions in data requirements for licensing versus reimbursement authorities Adapted from [14].

	Scope of evaluation	Internal versus external validity of data	Type of data preferred	Endpoints preferred
Licensing authorities	Benefit–risk of product under evaluation within the target indication	Efficacy focus; emphasis on a well-defined patient population	Randomized controlled trials	Surrogate or 'Hard'[a] endpoints
Reimbursement authorities	Relative efficacy and/or effectiveness compared with what is mostly commonly used in the disease area	Effectiveness focus; emphasis on internal and external	Randomized controlled trials and observational data, modeling of cost-effectiveness and budget impact, among others	'Hard'[a] endpoints and patient-reported outcomes (PRO) and/or health-related quality of life endpoints

[a] Refers to objectively measured health outcomes that drive costs (mortality, hospitalizations, among others).

environments, leading to uncertainty regarding health outcomes in the 'real-world' setting. However, reimbursement decisions must be based on how or if a product should be used and reimbursed within this world of uncertainty. Consequently, there is growing enthusiasm, especially among payers, for linking coverage and reimbursement of medical products to evidence of 'real-world' effectiveness, safety and/or health outcome measures. Designing a study suitable for licensing approval might not always translate to gaining favorable reimbursement. To account for these differences, decisions should be made with both audiences in mind, and additional tactics should be employed to demonstrate the comparative effectiveness (i.e. comparison of different interventions in a 'real-world' setting [12,13] of the product for a reimbursement audience).

Defining a target population

Reimbursement authorization to allow patient access to an intervention can include a narrower group than the licensed-approved population. The reimbursement agency could restrict usage to the patient groups or treatment settings where they believe the product is most effective and/or most cost-effective (e.g. the payer evidence standard), despite the indication in the product label. Many examples exist where the economic impact data do not meet the payer evidence standard. For example, submissions fail to identify a population representative of the countries' patients and/or provide (*post hoc*) analyses to determine a population where treatment is cost-effective. The submission should clearly identify the eligible patients, their point of treatment initiation, duration of therapy (e.g. acute or maintenance) and criteria for discontinuation if patients do not respond. Although accepted for licensing, the clinical evidence for the target population might not meet the criteria for effectiveness in real-world settings. Manufacturers should proactively identify the appropriate target population in their submissions in anticipation of restrictions from reimbursement authorities and to be able to broaden the scope of reimbursement in the future.

Choosing a comparator

Reimbursement agencies (especially those outside the USA) tend to prefer a comparison with the current standard of care, but the relevant standard of care often differs across markets. Submissions could fail because the selected comparator is not widely used within that country. The licensing authority does not require the comparison to be widely used or the one providing the most benefit [14]. For instance, the Food and Drug Administration (FDA) generally prefers more than one randomized, multicenter, placebo-controlled trial for a New Drug Application (NDA) submission. The European Medicines Agency (EMA) requires an active comparator (standard of care) and only accepts placebo if there is no marketed drug available. Thus, even regulators in different markets might not agree about the most appropriate comparator, but those interested in effectiveness generally agree on requiring a standard of care comparator.

Selecting the correct endpoints

Reimbursement authorities generally prefer 'hard' or objectively measured health outcomes that drive costs (stroke, mortality, among others); however, collecting these data might not be feasible before launch because they require long-term trials. For this reason, measurable, possibly surrogate, endpoints (e.g. walking

distance, lung function, tumor response and low-density lipoprotein level) are useful for licensing approval. To please both bodies, including surrogate trial endpoints that can be linked to 'hard' morbidity and/or mortality endpoints could be a suitable approach. In addition, selection of endpoints that demonstrate the differentiating features of a new product is important to fulfill reimbursement requirements for 'innovation' (section Current Evidence Requirements for Reimbursement for definition).

Consequences of neglecting HEOR evidence requirements

HEOR data have an important role in gaining or failing to gain reimbursement. For example, in the UK, the National Institute for Health and Clinical Excellence (NICE) has performed 207 appraisals in the past 10 years with 409 recommendations for action. Of those, 46 were not approved based on lack of available data [15]. Often, the rejections were owing to uncertainty in the economic evaluation, leading to wide ranges in incremental cost-effectiveness ratios (ICER) (i.e. a ratio of the incremental change in cost per unit of effectiveness when choosing a specific intervention relative to another intervention). The importance of robust HEOR evidence will become even more important in future assessments. NICE plans to introduce 'value-based pricing' in the UK in 2014, and Germany passed new legislation effective as of January 2011 mandating that manufacturers must provide evidence of an additional benefit compared with existing treatments to enter price negotiations. If the product is deemed to have no additional benefit; the product is immediately placed within a group of products with similar pharmaceutical and therapeutic characteristics for which maximum reimbursement prices have already been determined. Lack of sufficient data at the time of launch has also encouraged manufacturers to negotiate managed entry schemes [16,17][1] with payers in which either additional data must be collected or additional performance-based metrics must be met in return for access to the market.

Internal challenges in providing the evidence for successful product commercialization

The 'silo' structure of pharmaceutical companies and the resulting difficulties in communication, collaboration and resources allocation across groups is the primary internal challenge to successful evidence generation. The combination of talent, knowledge, team structure, tools and processes makes pharmaceutical companies successful and contributes to their innovation efforts to create products that can successfully reach the market [18]. Research and pharmaceutical company activities, however, are oftentimes individualistic and have a tendency to create 'knowledge silos' where teams are focused on their own objectives and might be hesitant to share information. This is particularly evident for the interaction between clinical research and development (R&D) and commercial and marketing. In addition, lack of information systems and processes might not capture and organize the internal knowledge appropriately [18,19].

Because pharmaceutical company personnel are segmented by function, teams often have different objectives for conducting research and utilizing resources. Merging R&D scientists and clinical professionals or clinical professionals and HEOR staff together in a collaborative working environment can be challenging. These partnerships, however, are crucial for successful evidence generation. Linking preclinical and clinical teams enables for a smoother transfer of information, ultimately helping the organization design clinical programs, fuel discovery and increase internal innovation to survive in an increasingly dynamic market [18]. Likewise the development teams need to be closely aligned with HEOR teams and with the commercial organization. HRQoL measures or healthcare utilization endpoints might not be required for licensing approval but might be crucial in addressing questions from other stakeholders (e.g. clinicians and reimbursement authorities), thus a collaborative approach enables optimization of data capture within and alongside the clinical development program. Some suggest that the 'silo' model will shift to a collaborative approach to improve R&D productivity, reduce costs, tap potential of emerging economies and switch from selling medicines to managing outcomes [19]. This shift is fueled by the current economic downturn combined with pressure from healthcare payers to maximize value for the money spent on medical products. To meet these demands and maximize internal resources, pharmaceutical companies might need to create new functions that span the entire development pathway or find other innovative ways to stimulate collaboration across groups. Education across functions about the purpose and needs of each team and setting objectives that encompass commercial success of the products could help mitigate antagonism and encourage teamwork. For instance, regulatory teams need to understand the purpose of HEOR endpoints in clinical trials and receive the assurance that these additional endpoints will be collected with the same scientific rigor as standard clinical measures to manage risk for licensing submissions. Finally, all stakeholders must understand the impact on market access if the evidence is not available at launch. If internal challenges can be met, pharmaceutical companies will be more successful in convincing healthcare decision makers of the value of their products.

External opportunities for providing the evidence for successful product commercialization

External opportunities for successful evidence generation include obtaining external advice and working towards international synchronization. Pharmaceutical companies have a relatively recent opportunity to seek advice from health authorities before their reimbursement submissions. Some health authorities have established consulting arms to help manufacturers focus on obtaining evidence that could lead to optimal reimbursement, including suggestions on whether more data are required, the specific patient population, appropriate comparators, among others. These meetings can be held as early as end of Phase II and can continue up until and/or after launch, but before submission for a payment decision.

Healthcare decision maker advice for a reimbursement submission might not alleviate problems of disparate data requirements from licensing authorities and payers, but the dichotomous standards set by these two stakeholders might be moving closer

[1] 'Managed entry' schemes are agreements between payers and pharmaceutical companies to diminish the impact on payers' budgets for new and existing schemes brought about by uncertainty and/or the need to work within finite budgets.

TABLE 3

Tactics to create the required evidence

	Task						
	Evidence gaps	**Unmet need**	**Target population**	**Patient benefit**	**Product innovation**	**Value for money**	**Communication**
Rationale	Reimbursement authorities might expect additional or distinct evidence from licensing authorities.	Prioritization for budget allocation across therapeutic areas.	Could be relevant for reimbursement authorities who might prefer 'innovation' in a subpopulation over treating all patients.	Patient-reported endpoints could be an important measure of product benefit. Licensing hurdles for PROs are high for label claims; need joint planning with clinical and HEOR to collect PRO data within trials.	Endpoints needed to differentiate the product and fulfill payers' requirements of 'innovation'. Reimbursement authorities are interested in morbidity and/or mortality endpoints that might not be available from short-term trials but can be collected from long-term studies.	Payers are willing to pay for value.	Make payers aware of the value of the product. Early communication with payers and KOLs before registration to ensure the right evidence is collected and the value messages are credible.

together. In the EMA's Road Map to 2015, the agency has specified a desire to engage with HTA agencies early in product development and throughout the lifecycle of the project for the two groups to be aligned [20]. Hence, discussions are ongoing to see how agency efforts could be more coordinated. At present, a pilot initiative involving clinicians, HTAs, patient representatives, payers, licensing authorities and drug developers from France, Germany, Italy, the Netherlands, Sweden, the UK and the EMA is under way to test the benefits of multi-stakeholder consultations early in the development phase to improve transparency and preparedness of all parties [21]. Furthermore, the Member States' HTA agencies and European Network for Health Technology Assessment (EUnetHTA) Joint Action have initiated a collaboration in which they will consider how the risks and benefits assessment contained in European Public Assessment Reports (EPAR) can contribute to relative effectiveness assessments undertaken by HTA bodies [22]. EUnetHTA Joint Action focuses on the development and evaluation of best practices for HTA methods and scientific cooperation among government-appointed organizations from EU Member States or other organizations that generate HTAs [23]. Collaboration with HTA agencies and streamlining of the development process also is an approach preferred by the European Commission's Directorate General for Health and Consumer (DG SANCO) [24]. In the USA in September 2010, the FDA and Centers for Medicare & Medicaid Services (CMS) collaborated on a memorandum of understanding on the issue of collaboration to consider establishing a process for overlapping review of new, 'innovative' medical products when the sponsor and both agencies agree to do so [25]. Although the details of this process are still being flushed out and the evidence standards required by each agency would not change, sponsors could request overlapping review in seeking a National Coverage Determination (NCD), the goal being non-duplicative submissions.

Thus, there are discussions occurring both in Europe and the USA with regard to harmonizing and standardizing the evidence needs of regulators and payers across settings [26]. There initiatives can provide a model for cross-collaboration within a product development organization to set up something similar within the organization.

Leveraging opportunities to create the required evidence and demonstrate value

Until harmonization efforts are fully operationalized, however, drug manufacturers need to satisfy the sometimes divergent needs of both licensing authorities and payers. This has been and continues to be crucial for survival in an environment where the time to market does not mean time to licensing but time to reimbursement. To gain market access, most drugs will need to obtain a positive reimbursement or coverage decision from payers in addition to satisfying requirements for licensing agencies. These aspects need to be clearly understood and supported with evidence (Table 3).

Create an interdisciplinary team to identify evidence gaps and establish unmet therapeutic need

Establishing a collaborative team, across clinical, regulatory, HEOR, marketing and branding, and allocating budget for planned activities are the first steps towards global strategic planning to

support the evidence generation process for the emerging product. It is the responsibility of the manufacturer to identify the therapeutic areas with the highest unmet need and to generate evidence to support the value of a new product in addressing an unmet need. Furthermore, manufacturers must determine the gaps between the types of data needed to satisfy licensing authorities and the type required for reimbursement authorities and develop tactics to address these needs. If identified early on, these evidence gaps can be strategically addressed by: (i) undertaking market research, competitive intelligence and payer research to establish a better understanding of practice and treatment patterns and unmet need in key countries; (ii) integrating HEOR endpoints into the clinical trial program of the product (i.e. building utility or HRQoL measures or resource use collection into clinical trials); (iii) initiating scientific advisory meetings to help prioritize the endpoints that matter the most to key stakeholders and fulfill the unmet needs; or (iv) securing time and funding to conduct additional studies, which can be run in parallel to the clinical development program, to meet the needs of reimbursement authorities or to shape and prepare the market by highlighting the unmet medical need, patient suffering and cost to society.

Regardless of the strategies used to overcome these data gaps, identifying and prioritizing them ensures optimal preparedness that can help meet the ever-changing requests of reimbursement authorities and can result in efficiencies and/or cost savings by designing studies that can include both clinical and HEOR outcomes (i.e. a safety registry for EMA requirements could include HEOR data, such as HRQoL surveys and resource use data collection at the same time). Ultimately, manufacturers must be prepared to provide a range of evidence that can fulfill both licensing and reimbursement authority needs at the right times, whether the focus is efficacy studies with high internal validity, effectiveness studies with high external validity, or a combination of the two. Recent literature has suggested that these concepts are not necessarily dichotomous, and the true gold standard for evaluating new therapies is to consider a 'body of evidence' that includes both RCTs and observational studies [27].

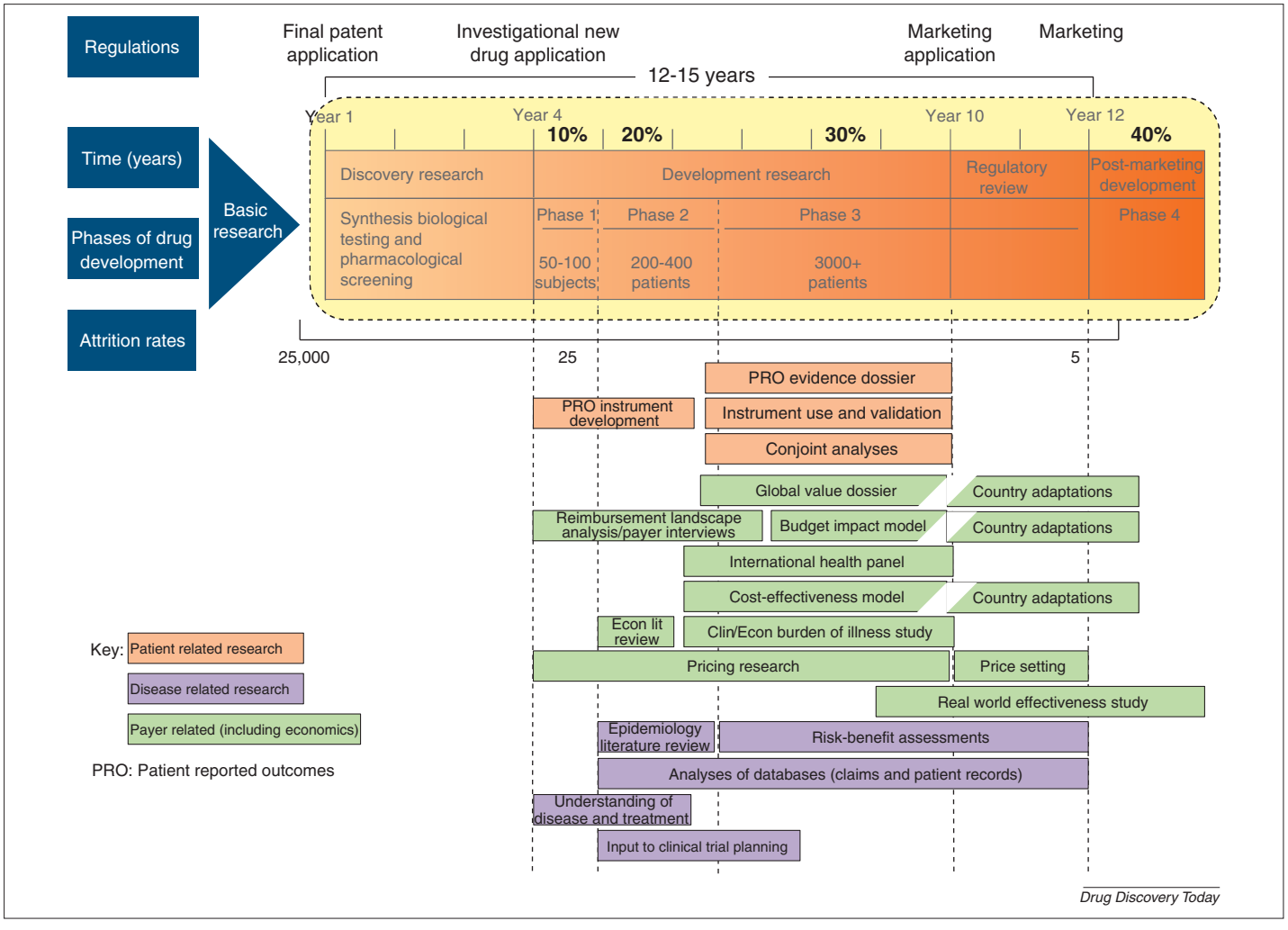

FIGURE 1

Generic timeline for product development and percentage of involvement of HEOR in each phase. *Note*: Timing of patent application may vary by country and manufacturer.

Adapted from [graph © Association of the British Pharmaceutical Industry (www.abpi.org.uk) with additional information provided by United BioSource Corporation].

Identify target population

Patient subsets remain an area of high value for reimbursement authorities. Payers seek to target therapies to those most likely to benefit and subsequently minimize budget impact. Identifying subpopulations could be achieved by using a novel endpoint or strategic trial design that enables the identification of population subsets who respond better or worse to treatment. Manufacturers also can consider trial simulation to generate quantitative estimates of success among different patient populations to mitigate the risk of investing in a large clinical trial. When sponsors can establish target populations that are accepted by payers, a further question remains as to whether prescribers will stay within the desired reimbursement bounds in actual practice. This has led to demands for manufacturers to collect data to demonstrate that the product has stayed within the target bounds. Planning for such studies should be considered early in the development process, because presenting these designs within a reimbursement submission could convert a probably negative response into a positive one.

Establish patient benefit

Demonstration of patient benefit can sometimes offer more support for the value of a new product in certain therapeutic areas than laboratory markers, acting as surrogate endpoints, such as hemoglobin A1c or high-density lipoprotein levels, because the patient improvement fulfills the unmet need more than a biomarker (e.g. in irritable bowel syndrome or chronic constipation). Licensing hurdles for PROs, however, are high and necessitate advance planning to select the appropriate validated tool and to capture the necessary evidence.

Demonstrate product innovation

Although the operable definition of innovation might be unclear or inconsistent across laws, regulations and policies, demonstrating the innovation of the product is necessary to secure market access. NICE in the UK suggests that an innovative product is one that is new, offers an improvement compared with existing therapies, and provides 'a step-change in terms of outcomes for patients [28]'. However, innovation is multifaceted, and manufacturers must determine the types of innovation, such as commercial, technological and therapeutic, that matter most to reimbursement authorities [11,29]. Clarification of the definitions of innovation as they relate to market access, investment in the development of products that meet those requirements, and subsequent positioning of the differentiating features associated with innovation are crucial to justify premium pricing.

Establish value for money

Economic studies based on the clinical trial results, where with foresight the appropriate data were collected and linked to include long-term outcomes using database analyses or longitudinal studies, will support the value for money of the product and encourage payers to fund it. Careful planning in Phases I–III will enable for the generation of valid cost-effectiveness analyses, budget impact analyses and estimates of the impact of the product on overall treatment costs that can be used in submissions to payers and HTAs.

Communicate the evidence to the 'right' audience at the 'right' time

Planning for evidence generation should begin in Phase I and be a dynamic and iterative process that will be updated throughout the product lifecycle to reflect new internal data in addition to the latest external pressures (Fig. 1). These activities must be prioritized appropriately so that the internal stakeholders (clinical, HEOR, marketing, among others) are well coordinated and so that the right evidence is available at the right time.

Concluding remarks

The need for appropriate evidence generation requires sufficient and careful preparation. Planning for evidence generation should begin in Phase I and be considered a 'living' process that can be updated throughout the product lifecycle to reflect new internal data in addition to the latest external demands. For pharmaceutical companies to be successful in creating the required evidence, communication and collaboration across pharmaceutical functions is crucial. The break-out from the silo mentality is crucial, as is the establishment of multi-functional teams that include clinical, regulatory, HEOR and commercial.

This information is written as a general guide, so we recommend that specific professional advice is sought before any action is taken.

Disclosure

United BioSource Corporation received funding from Astellas Pharma to conduct this study.

Acknowledgements

We would like to thank Ruth Brown (United BioSource Corporation) and Rob Thwaites (United BioSource Corporation) for their valuable comments on the manuscript. We would like to thank the United BioSource Corporation production team for their assistance in preparing the manuscript for submission.

References

1 Goetghebeur, M.M. *et al.* (2008) Evidence and Value: Impact on DEcisionMaking – the EVIDEM framework and potential applications. *BMC Health Serv. Res.* 8, 270

2 Jewell, C.J. and Bero, L.A. (2008) Developing good taste in evidence: facilitators of and hindrances to evidence-informed health policymaking in state government. *Milbank Q.* 86, 177–208

3 Eddy, D.M. (1990) Clinical decision making: from theory to practice. Anatomy of a decision. *JAMA* 263, 441–443

4 Eddy, D. (2007) Reflections on science, judgment, and value in evidence-based decision making: a conversation with David Eddy by Sean R. Tunis. *Health Aff. (Millwood)* 26, W500–W515

5 Neumann, P.J. *et al.* (2008) Medicare's national coverage decisions for technologies, 1999–2007. *Health Aff. (Millwood)* 27, 1620–1631

6 PBAC, (2006) *Public Summary Document: Nicotinic Acid.*

7 Scottish Medicines Consortium. (2010) Glucosamine sulphate 1,500 mg powder for oral solution (Glusartel®). SMC No. (647/10)

8 CADTH, (2009) *CEDAC Final Recommendation on Reconsideration and Reasons for Recommendation: Dabigatran Etexilate.*

9 Chambers, J.D. and Neumann, P.J. (2010) US healthcare reform: implications for health economics and outcomes research. *Expert Rev. Pharmacoecon. Outcomes Res.* 10, 215–216

10 Annemans, L. (2010) *Making Innovative Drugs Accessible in the European Union: Recommendations from the Belgian EU Presidency*. ISPOR (accessed November 2010) http://www.ispor.org/congresses/prague1110/ReleasedPresentations/Lieven-Annemans-Slides.pdf

11 Morgan, S. *et al.* (2008) Towards a definition of pharmaceutical innovation. *Open Med.* 2, e4–e7

12 Garrison, L.P. *et al.* (2010) A flexible approach to evidentiary standards for comparative effectiveness research. *Health Aff. (Millwood)* 29, 1812–1817

13 US Department of Health and Human Services, (2011) *Draft Definition, Prioritization Criteria, and Strategic Framework for Public Comment.*

14 Lonngren, T. (2010) Successes and challenges in drug development – a regulatory perspective. *Presentation given at 16th World Congress on Basic and Clinical Pharmacology*, Copenhagen, Denmark, 17–23, July

15 National Institute for Health and Clinical Excellence (NICE), (2010) *Technology Assessment (TA) Decision Table*.

16 Carlson, J.J. *et al.* (2010) Linking payment to health outcomes: a taxonomy and examination of performance-based reimbursement schemes between healthcare payers and manufacturers. *Health Policy* 96, 179–190

17 Adamski, J. *et al.* (2010) Risk sharing arrangements for pharmaceuticals: potential considerations and recommendations for European payers. *BMC Health Serv. Res.* 10, 153

18 Wang, A.E. (2003) *Rx for Pharmaceutical Companies: Internal Collaboration is the Key to Improved Innovation.* IBM Institute for Business Value

19 PricewaterhouseCoopers, (2010) *Biotech Reinvented: Where Do You Go from Here?*

20 European Medicines Agency, (2010) *Road Map to 2015: The Agency's Contribution to Science, Medicines, Health. Draft for Public Consultation*.

21 Tapestry Network Pilots of multi-stakeholder consultations in early-stage drug development, http://www.tapestrynetworks.com/documents/EHILN-multi-stakeholder%20pilots%20joint%20statement%20-%2010-19-10.pdf.

22 European Network for Health Technology Assessment (EUNETHTA), (2010) *European Medicines Agency and EUnetHTA Joint Action Start Collaboration on European Public Assessment Report (EPAR) Contribution to Relative Effectiveness Assessments*. In: http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/02/WC500073909.pdf

23 European Network for Health Technology Assessment. (2011), http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/02/WC500073909.pdf

24 Directorate-General for Health & Consumers, (2008) Future developments for the European Collaboration on Health Technology Assessment. *Presentation given at EUnetHTA Conference*, Paris France, 20 November

25 US Food and Drug Administration, (2010) *Memorandum of Understanding Between United States Food and Drug Administration and Centers for Medicare and Medicaid Services*. In: http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm217585.htm

26 Eichler, H.G. *et al.* (2010) Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. *Nat. Rev. Drug Discov.* 9, 277–291

27 Fleurence, R.L. *et al.* (2010) The critical role of observational evidence in comparative effectiveness research. *Health Aff. (Millwood)* 29, 1826–1833

28 Kennedy, I. (2009) *Appraising the Value of Innovation and Other Benefits. A Short Study for NICE.* National Institute for Health and Clinical Excellence

29 Kopp, C. (2002) What is a truly innovative drug? New definition from the International Society of Drug Bulletins. *Can. Fam. Physician* 48, 1413–1415

30 International Society for Pharmacoeconomics and Outcomes Research. Global Health Care Systems Road Map, http://www.ispor.org/htaroadmaps/default.asp

31 Motola, D. *et al.* (2005) Therapeutic innovation in the European Union: analysis of the drugs approved by the EMEA between 1995 and 2003. *Br. J. Clin. Pharmacol.* 59, 475–478