

EXECUTIVE SUMMARY

Objective

The purpose of this report is to identify the role and contribution of health economics activities in supporting the product life cycle of a drug, in other words the role and contribution of health economics activities to drug development, reimbursement and market support. Health economics activities are as important for successful product development, reimbursement and market support as the evaluation of clinical outcomes and consequent arguments for the place in therapy of a new product.

This report identifies not only the clusters of health economic activities that should accompany drug development from discovery through to marketing approval but also those activities that are critical to successful market reimbursement, market entry and the support of the product through the balance of the product life cycle. The number of activities identified is daunting and, for those unfamiliar with the potential contribution of health economics to support the drug life cycle, that may come as a revelation. Incidentally, the term 'health economics' is used in this report rather than the more current terms 'pharmaceutical economics' or 'pharmacoeconomics'; the reason is that the role of health economics is greater and encompasses more activities than those typically associated with 'pharmaceutical economics' or 'pharmacoeconomics'.

In addition, this report provides the framework for making a value or business opportunity assessment (BOA) of a drug product. Health economics activities should not be seen as *ad hoc* or add-ons to the drug development process. The activities identified here are fundamental to establishing the business case for a product and for re-evaluating the business case at key go/no-go decision points in drug development and market entry. Just as the business case for a new compound has to be made to an internal audience – senior management and corporate officers within a drug company – so the framework presented here can be seen as the basis for making a business case for a product to an external audience. Hence, this report is just as useful to the smaller biotechnology companies who are seeking to make a value case for their product to future partners as it is to larger manufacturers concerned to maximise the value of their pipeline.

As a primer for both established pharmaceutical manufacturers and the smaller drug development and biotechnology companies the key message is that health economics can create substantial value added – as well as providing the basis for early decisions to continue or abandon product development.

As will be emphasised, value added in a drug product comes from two sources: (1) establishing market potential in the context of total cost pricing and (2) the choice of a unit price that creates a potential win-win situation between the manufacturer and the purchaser or prescriber of the drug, thus ensuring early product reimbursement, rapid product uptake and maximum market share. If these propositions are accepted and factored into the BOA at an early stage in product development then a more realistic picture of market opportunities and the potential for reimbursement will emerge.

In the last resort, health economics analyses in drug development have one objective: to identify a sustainable price for a product in a target health-care environment or market segment. This is achieved by taking a total cost of health-care approach and building, from the early stages in drug development, pricing models that reflect a comprehensive understanding of treatment prevalence in disease areas, the patterns and costs of health-care delivery and, most importantly, the budget impact of alternative pricing and marketing scenarios.

In this approach, health economics is no longer seen as a late phase III add-on to an essentially clinical programme in new drug development. Rather, it is an essential part of

the drug development process from pre-phase I through to post-market-entry life cycle support.

Importantly, health economic analyses provide the needed reality check on the all too often over-optimistic marketing claims for new drugs; business opportunity claims that can result in the misallocation of millions of dollars in product life cycle investment. If this reality check is to be successful it requires a sophisticated and comprehensive framework for the evaluation of business opportunities.

A critical element in product valuation is taking explicit account of uncertainty in the business opportunity assessment model. This is achieved, as will be argued here, through framing the assessment in terms of simulation rather than sensitivity modelling. While simulation modelling – the application of Monte Carlo techniques – is applied widely in business decisions and process assessment, it has particular relevance to the evaluation of drug products. Evaluations of market potential typically take place in relatively poor information environments and in situations where predictions as to market potential are open to substantial revision as the drug development process unrolls. Data are limited on key inputs: disease prevalence, treating prevalence, treatment patterns and costs. The performance of a new compound and reasonable assumptions as to its potential place in therapy typically await phase II and, more importantly, phase IIIA trial results, hence the need to take explicit account of uncertainty in framing the business case for a new product.

In focusing upon treatment patterns, cost of care and the budget impact of therapies within health-care systems, health economics analyses in the early stages of drug development provide the critical reality check for drug development. Rather than relying upon poorly designed and wish fulfilling ‘soft’ market research to support claims for projected market share and profit contribution in business opportunity assessment spreadsheets, health economics assessments establish from day 1 what the market parameters are for a new product. These parameters – based on estimates of treating prevalence and treatment costs in key markets and market segments – are critical to early go/no-go decisions for product investment.

As the drug development process unrolls, the range and intensity of health economics activities increases substantially. Activities include developing mock reimbursement submissions, pricing models, comparator evaluations for phase IIIA efficacy and phase IIIB effectiveness trial designs and budget impact assessments for key markets and market segments. Health economics activities not only support the drug development process, they are also critical in supporting reimbursement applications and supporting the product once market entry has been achieved.

Embracing health economics

With few exceptions, pharmaceutical manufacturers have yet to embrace health economics as a core discipline in the drug development process. All too often, health economics is seen as an activity that can be safely neglected until decisions are being made for phase III trial design; indeed, in many cases it is considered an activity that is best left until marketing approval has been received and a price has been determined. The health economist is then faced with what is, in effect, a *fait accompli*: the price has been determined, claims have been made for anticipated market share and the bottom line contribution of the new product. While these may, in retrospect, be seen to be inconsistent, the health economist is charged with making a cost-effectiveness case for the product and in taking ultimate responsibility for ensuring reimbursement. Not surprisingly, reimbursement applications often fail and what was touted as a blockbuster product (often aided and abetted by analysts who should know better) ends up as a niche product. Given the increasingly rigorous analytical and evidentiary standards being set by reimbursers, this ‘reimbursement only’ strategy for health economics inputs is extremely risky.

In short, to treat health-economics-related tasks and activities as a post-phase-III add-on to the drug development process is courting failure – at worst an overpriced drug with a

trivial market share, at best a continual struggle to convince sceptical reimbursers that a drug has a place on formulary.

The task of the drug manufacturer is made even more difficult by the changing focus of health economics from a traditional cost-effectiveness or cost–outcomes focus to what has been described as a systems-impact perspective; from a focus on decision-model-based cost-effectiveness claims to the more difficult to substantiate claims for ‘affordability’ by health-care systems. This is now changing, with the focus extending to the role of health economics over the life cycle of a drug product.

The increasingly cost-conscious nature of formulary decisions and the willingness of reimbursers to reject a drug for listing on budget impact grounds mean that drug companies are having to address the issue of ‘affordability’ at a very early stage in the drug development process. Indeed, the decision as to whether or not to invest resources in the pre-phase-I development process should be driven by precisely this consideration. Hence the importance of seeing health economics activities as integral to the drug development process; as an integral part of business opportunity assessments and the equal of those activities on the clinical side, from phase I through phase IIIB, that have historically driven the development process.

Winning the health economics case

How do drug manufacturers and biotechnology companies ‘win’ the health economics case? How do they establish the value case for a new product and ensure its acceptance at a price consistent with a minimum acceptable rate of return? The simplest answer is to become experts, not only in the clinical aspects of drug design and development but in understanding, from a treating prevalence, resource utilisation and cost perspective, how care is delivered (and the potential for a new product) in that treating environment. This is not something that can be determined and driven with results from highly aggregative randomised clinical trials – and supported by one or two peer-reviewed papers arguing for product ‘cost-effectiveness’. Manufacturers must understand their customers and their customers’ needs. The only way to do this is to invest the resources in the health economics activities recommended in this monograph.

Structure of this report

Chapter 1: The pricing and reimbursement decision

The focus of Chapter 1 is on introducing key concepts and describing how health economics activities map into the clinical phases of drug development. The chapter begins with an overview of the role of health economics in product development – this leads to a detailed mapping of health economic activity ‘clusters’ into the principal clinical phase of product development.

The framework for evaluating the ‘value’ proposition for a new product is the BOA. The role of a BOA is described, with the emphasis upon how it should be structured and the key data inputs for evaluating market potential. An important caveat: at such an early stage in drug development any attempt to specify a complete BOA is a waste of time. At best, the focus should be on the aggregate size of the present market for that indication and the share that would need to be captured to justify investment in a new compound.

Ultimately, as described in Chapter 1, the BOA (which should be seen as a dynamic, evolving decision tool) sets the stage for a reimbursement application. It is emphasised that a BOA is built up from country- and market-segment-specific BOAs. These reflect the characteristics of local markets and set the stage for a global pricing strategy. Current issues and concerns in the reimbursement process are discussed, in particular the increasingly stringent analytical and evidentiary standards that are being put in place by formulary committees.

Reimbursement leads naturally to pricing. As noted, pricing must be centre-stage at even the earliest stages of drug development. Populating a BOA with a poorly justified unit pricing assumption is unacceptable. The focus must be on the notion of an ‘affordable’ price – one that is acceptable to the payer in cost-effectiveness and budget

impact terms. This is tied in with the issue of the 'message' a manufacturer wants to take to the market. Questions addressed include:

- What is the message that is appropriate for customers, whether they be national reimbursement committees, managed care or medical practices?
- Should we only be concerned with formulating a modelling-based claim for incremental cost effectiveness or should we also recognise the issue of affordability?
- Is affordability more important than claims for cost-effectiveness?
- Is the message on cost-effectiveness or affordability to be delivered for specific target populations?
- Should we anticipate attempts by reimbursement agencies to restrict use to sub-populations?

Chapter 1 concludes with an overview of market prioritisation and the dominance of the US market in any evaluation of market potential, with the caveat that the US market is (by world standards) highly segmented (a fact that has to be considered in valuing US market opportunities).

Chapter 2: Cost-outcomes claims and budget impact assessments

In Chapter 2 the issue of cost-effectiveness versus affordability (the traditional versus the systems approach to health impact assessment) is discussed in detail. The importance of meeting evidentiary and analytical standards in health economic evaluations for reimbursement applications is reviewed in the context of the Australian guidelines.

As part of the drug development process, it is proposed that mock reimbursement submissions be prepared for all key markets and market segments; a template for such a mock reimbursement submission is presented. The links between a mock reimbursement submission and a BOA are detailed, together with a brief review of the role of simulation modelling in both.

Chapter 3: Clinical pre-phase-II – health economics activities

In Chapter 3 the recommended health economics stages and activities cluster for the pre-phase-II drug development period are described. The emphasis is on completing a foundation health economics assessment, with a revision, the first revised health economics assessment, following phase I trials as part of the decision to proceed to phase II trials. Such an assessment is, of course, nothing more than the 'value case' for the product; a value case that is revisited as the basis for either go/no-go investment decisions by a manufacturer or a partnership/sales decision by a biotechnology company.

Key activities that form the core of all the economic assessments accompanying product development are ongoing evaluations of treatment prevalence and treatment patterns, an ongoing health economics literature review and its corollary a pooled analysis of comparator/competitor therapies, an ongoing review of input pricing options for modelling, an ongoing review of treatment costs and their implications for pricing options for the new product and, not least, the ongoing process of updating the business opportunity assessment for the product.

Chapter 4: Clinical phase II – health economics activities

Chapter 4 is concerned with health economics activities associated with clinical phase II in drug development. Critical to this stage, which focuses on the preliminary cost-effectiveness case for the product, is a review of dosages and product formulations (which can be critical in determining drug costs and treatment costs), an evaluation of the outcome measures appropriate to this disease state, the contribution of a quality of life claim and the question of investing in a quality of life instrument. Following the phase

II trials, there is a further review of the health economics input to the decision to go to phase III; a second revised health economics assessment. A key element in the identified health economics activities is the preparation of a mock reimbursement submission.

Chapter 5: Clinical phase III (phase IIIA) – health economics activities

'Getting it right' at phase IIIA is critical to drug development and market entry. The contribution of health economics activities described in Chapter 5 are:

- Health economics inputs to phase IIIA protocols
- Health economics training for liaison staff
- The third revised health economics assessment, which occurs once the phase IIIA trial results have been released
- A preliminary evaluation of the cost-effectiveness claims for the product given the clinical outcomes reported from phase IIIA.

This chapter also considers the requirements for health economics training directed towards product and regional managers and medical liaison staff.

Chapter 6: Clinical phase IIIB and pre-market-entry – health economics activities

This chapter is concerned with the health economics activities associated with the phase IIIB trial programme, in particular the possibility of a decision to invest in effectiveness or naturalistic trials. The chapter starts with activities concerned with specifying the health economics requirements of phase IIIB trials and evaluating the results of these trials. This is followed by the tasks associated with finalising the health economics case for the product – with the principal focus on preparing reimbursement submissions. The chapter concludes with a review of activities to support the implementation of sales training for the health economics case.

Chapter 7: Formulary approval, clinical phase IV and post-market-entry – health economics activities

The initial focus here is on making and monitoring the reimbursement application. Once reimbursement has been achieved, the focus shifts to those activities required to monitor product status and the implementation of health economics activities to maintain product status – market share, formulary positioning and price.

Chapter 8: Summary and conclusions

The final chapter provides an overview of the health economics activity clusters described in Chapters 3–7, with concluding comments on the management of health economics activities and their contribution, both to manufacturers as well as to biotechnology companies, in making the value case for a product to both internal and external audiences.