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HEALTH POLICY ANALYSIS

Early Dialogue Between the Developers of New Technologies and Pricing and Reimbursement Agencies: A Pilot Study

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ABSTRACT

It is common practice for developers of new health care technologies to engage in early dialogue with the major regulatory agencies; such discussions frequently center around the proposed clinical trial designs to support the registration of new interventions and suggestions on their improvement. Pricing and reimbursement agencies are increasingly using the results from health technology assessments to inform their decision making for new technologies. Such assessments are invariably underpinned by the phase 3 clinical trial evidence which may not provide answers to the key questions. Technology developers are beginning to realize that direct, early dialogue on the evidence requirements of the major pricing and reimbursement agencies, before phase 3 clinical trial designs for their key development compounds have been finalized, may be beneficial. This article reports on the pioneering efforts of one technology developer in seeking early dialogue with seven pricing and reimbursement agencies in five countries globally in 2007–2008 on their likely evidence requirements for a new oral treatment for patients with chronic plaque psoriasis. The pilot project demonstrated that a feasible process of early dialogue could be established, through a face-to-face meeting with prior circulation of a briefing book. Although there was some variation in the advice the similarities far outweighed the differences. More experience of early dialogue needs to be accumulated, involving a wider range of pricing and reimbursement agencies and compounds. The conclusion of this study, however, was that early dialogue can be a worthwhile process for all parties and can lead to a common understanding about evidence development for market access.

Keywords: cost-effectiveness analysis, clinical research, pharmaceuticals, decision-making, payer direct engagement.

Introduction

It has been common practice for several years for the developers of new health care technologies (primarily new pharmaceuticals) to engage in early dialogue with regulators, such as the US Food and Drug Administration. The reasons for this are self-evident. Given the large and costly investment in clinical research and development to establish the efficacy and safety of a new product, it is important for the company to be reasonably certain that, if research of an adequate quality is conducted, approval to market will be granted if the net clinical benefit is considered to be positive. Therefore, technology developers often present their proposed clinical trial designs to regulators in order to obtain feedback and to receive suggestions on their improvement.

A more recent development is that in several jurisdictions a health technology assessment, including an economic evaluation, is now required as part of the processes for determining the price and reimbursement status for new technologies. In these jurisdictions the process is that the sponsor of a new technology prepares a submission containing such an evaluation, according to an agreed set of guidelines [1]. Although the published guidelines give some clues as to the scientific quality of clinical and economic evidence that may be required, they do not provide sufficient detail to answer important strategic questions such as "to obtain reimbursement for first line use in a given category of patients, precisely what evidence should be submitted?" This is understandable, given they are not written for this purpose; they are written to help potential applicants prepare a submission from the evidence that has already been generated rather than specifying, before the event, what evidence should be generated.

Although the requirements for the submission of evidence to pricing and reimbursement agencies do not have the same legal status as submissions to regulators, from the manufacturer's perspective they are gaining increasing importance, because they are critical for market access for a new product. Market access, not product licensing, is the ultimate goal, and technology developers are increasingly viewing the clinical development program as providing data for both purposes.

A potential complication is that the evidence required for a pricing and reimbursement submission might involve the production of clinical data that go beyond that required for a regulatory

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submission. For example, in order to obtain reimbursement for first line therapy, it may well be necessary to demonstrate the product is more efficacious than an existing first line therapy, or it may be necessary to collect data on an outcome that is of interest to a pricing and reimbursement agency, although not required by a regulator. For example, some new anticancer drugs have obtained regulatory approval (in some jurisdictions) based on demonstration of improvements in progression-free survival, whereas some pricing and reimbursement agencies would likely require evidence on overall survival, unless they can be convinced that the relationship between the two outcomes has been well established [2–4].

Therefore, a growing number of technology developers have realized that a dialogue on evidence requirements may be beneficial with pricing and reimbursement agencies before phase 3 trial designs are finalized with regulators [5]. This article reports on the pioneering efforts of one technology developer in seeking early dialogue with several pricing and reimbursement agencies. It reflects on the main lessons learned and considers future directions and challenges.

Methods

General approach

An approach was made to seven pricing and reimbursement agencies in five countries globally in order to establish whether they would be open to early dialogue. The agencies concerned varied in their remit and here the terms "pricing and reimbursement agency," "health technology assessment agency" or "payer" are being used interchangeably. Some of the agencies were directly involved in determining reimbursement status, such as listing of drugs on the national or regional formulary. Others merely issued general guidance on the use of products within the country's health care system, which could be mandatory or not. Some had a role in price negotiations, others not. However, the common feature of all the agencies approached was that they were known to be interested in the role of health technology assessment in helping determine the appropriate use of treatments to obtain a comparative health gain within their health care system. They were selected either because they were agencies in large pharmaceutical markets, or because they had an established track record in using economic evaluation to inform reimbursement decisions.

The agencies were asked questions about the likely evidence requirements for a development compound that might be the subject of a pricing and reimbursement submission sometime in the future. A briefing book was produced, giving some background on the compound, its planned positioning in current and anticipated future treatment pathways and outlining several key questions on which the company required responses.

The questions related to various aspects of the proposed phase 3 clinical trials, such as;

- What is the most relevant target population for this therapy;
- With which alternative therapies should this drug be compared;
- What outcomes (e.g., clinical, quality of life) should be measured;
- Over what time period should measurement be made (i.e., length of patient follow-up);
- Should the issue of non-responders be examined and how should "non-response" or "treatment failure" be defined;
- Are there relevant subgroups of the patient population that should be considered?

In each case the agency concerned determined the precise nature of the provision of early dialogue (e.g., informal conversation or formal meeting) and the nature of the feedback given (e.g., written advice or not). The similarities and differences of the various approaches to early dialogue and the variations in the advice offered were noted.

The development compound

The compound chosen for the study was a new orally active treatment for patients with chronic plaque psoriasis. This choice was based on several considerations: 1) (plaque) psoriasis was an important disease area for the company at the time, with four compounds in development; 2) the compound was thought to have considerable commercial potential; 3) (plaque) psoriasis was considered to be a major disease with a high level of unmet need; 4) the compound was in the right (i.e., early) stage of clinical development, with the major phase 2 and phase 3 clinical trials still at the design stage; 5) new products for patients with plaque psoriasis had recently been launched, some of which had been subjected to rigorous health technology assessments; 6) internal documentation already existed that could form the basis of the briefing book and there was general support in the company for the study; and 7) there were several important unresolved issues about the positioning of the compound and the nature of the clinical development program that would be required.

Briefing book

A similar briefing book was used for all the meetings. This covered the overall meeting rationale and objectives (from the company's viewpoint) and background on current treatment options for patients with chronic plaque psoriasis (see Fig. 1 for an example of presenting clinical management pathways for the purpose of pinpointing new treatment positioning options). The briefing book also discussed issues arising from the technology assessments on the recently launched products (e.g., the anti-tumor necrosis factors), the data currently available on the development compound, and the company's draft plans for future evidence generation.

The latter items were the most important because they represented expensive decisions that were largely irreversible once the trial designs had been set. Therefore, a substantial amount of detail was given on the design of the planned phase 2 (dose finding) trials and the guidance that the company had received from regulatory agencies on the design of the planned phase 3 clinical trials. Finally, a few proposed phase 3 clinical trial designs were presented, including diagrammatic representations.

This information formed the backdrop for a discussion with the agencies included in the pilot study. In the case of those agencies that use the results of economic evaluations to make pricing or reimbursement decisions, discussions also took place on the company's outline plans for economic evaluation and a series of specific questions. Some of these dealt with specific scientific issues (e.g., the method for determining utility estimates), but the most important ones addressed strategic issues like 'if the company's aspiration is for the compound to be used first line for both the short-term treatment and long-term control of adults with chronic plaque psoriasis who are candidates for systemic therapy, what types of comparative clinical and economic evidence would best support it?'

Results

Agencies surveyed

All the seven agencies approached agreed to participate in the exercise, and the meetings took place between November 2007 and June