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Assessing prescription medications for priority regulatory review

Nigel S.B. Rawson *

Center for Health Care Policy and Evaluation, Eden Prairie, MN, USA

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Abstract

Poor concordance exists between medications that receive a priority review in Canada and those given an expeditious review in the United States. The objectives of this study were to obtain an evaluation of the clinical significance of new drugs approved in both countries from expert clinical pharmacologists, and to examine the concordance of their aggregate assessment with whether or not the product received an expeditious review in either country. Five experts assessed 146 new medications approved in both Canada and the United States between 1996 and early 2002. Overall, the concordance between the experts' assessments was poor and there was large variation in products considered to be of sufficient importance for priority status. Nevertheless, the experts' evaluations suggested that several priority-reviewed products did not warrant such a review. Regulatory agencies select new medications of potential clinical significance to receive shorter review times to minimize the delay in access to them, but, in Canada, only a low proportion of priority-status products had review times within Health Canada's performance target. The large variation in the assessment of clinical significance suggests that a more appropriate strategy in Canada is to devote sufficient resources to reviewing all medications in a timely manner.

Keywords: Priority review; Clinical significance; Canada; United States

1. Introduction

In an attempt to facilitate timely access to new medications of potential clinical significance, the US Food and Drug Administration (FDA) introduced a procedure in 1992 in which drug applications are evaluated early in the review process for suitability for priority status. For a priority review, a drug must provide "a significant improvement, compared to marketed products, in the treatment, diagnosis or prevention of a disease" (Center for Drug Evaluation and Research, 1996). Improvement should be demonstrated by evidence of increased effectiveness in treatment, prevention or diagnosis of disease, elimination or substantial reduction of a treatment-limiting drug reaction, documented enhancement of patient compliance, or evidence of safety and effectiveness in a new sub-population. Priority-status products have a shorter review time performance standard; 90% to be reviewed within 6 months compared with 90% within 10 months for standard reviews, time being measured as that during which FDA staff are actually working on the application ("FDA time") and not the total time between the submission of the application and approval for marketing.

The FDA has two other mechanisms to facilitate the development of treatments for serious and life-threatening conditions: accelerated approval, implemented in 1993 and codified in the FDA Modernization Act of 1997, and fast track, which is a provision of the Act. A treatment with a significant benefit over existing therapies may receive accelerated approval based on its effect on a surrogate endpoint or an endpoint other than

* Present address: GlaxoSmithKline, 2030 Bristol Circle, Oakville, Ont., Canada L6H 5V2. Fax: +1 905 829 6065.
E-mail address: nigel.s.rawson@gsk.com.

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survival or morbidity, or it can be approved with restrictions to promote safe use. Therapies that receive fast track approval are those with the potential to treat patients with serious or life-threatening disorders whose needs are not presently being met. The fast track program has several benefits throughout the development and approval phases (Milne and Bergman, 2001). Although both programs are distinct from the priority-status designation, products in all three programs are generally reviewed more expeditiously.

In 2002, as part of its efforts to improve the nation's ability to respond to emergencies, the FDA introduced the Animal Efficacy Rule, which describes the setting where animal model data may be used in place of clinical trial data to support efficacy claims for serious diseases that cannot be studied in humans (Food and Drug Administration, 2002). The first product to be approved under this rule is pyridostigmine bromide used as a pretreatment to increase survival after exposure to Soman "nerve gas" poisoning (Center for Drug Evaluation and Research, 2003).

Health Canada also has a priority review system, which began in 1996 (Therapeutic Products Directorate, 2002). The Canadian criteria are close to those of the FDA and the performance standard for priority-status medications (225 calendar days) is also shorter than the standard review target (355 calendar days). Until recently, these performance standards were for the duration between the receipt of an application and approval for marketing approval, but they are now for the time between the application being received and Health Canada's first response to it (Rawson, 2003). To obtain priority status in Canada, the manufacturer must submit an application to Health Canada. An application process may deter companies from having their products considered for this status. Nevertheless, if the systems are to be considered meaningful in giving priority to medications of therapeutic significance and the attempts to move towards international harmonization are to be deemed successful, one would expect a large proportion of the products that receive an expeditious review in the United States also to receive a priority review in Canada.

However, this is not the case. Of 146 new medications approved in both Canada and the United States between 1996 and early 2002, 59 received an expeditious review in the United States but only 31 (53%) of these were given priority status in Canada. In addition, 6 (16%) of the 37 Canadian priority-reviewed products did not receive an expeditious review in the United States. The objectives of this study were, therefore, to obtain an evaluation of the clinical significance of a large set of new drugs approved in Canada and the United States from expert clinical pharmacologists, and to examine the concordance of their aggregate assessment with whether or not the product received an expeditious review in either country.

2. Methods

The time to review and approve new drugs in Canada and other countries (including the United States) between 1996 and 2001 has been evaluated previously, with similar data collection methods (Rawson, 2000, 2003; Rawson and Kaitin, 2003). In this prior work, a "new drug" was defined as any new active substance (chemical and biological), except diagnostic products, new salts, esters, isomers and dosage forms of already marketed drugs, and combinations containing previously approved substances. Drugs approved as over-the-counter products were excluded.

From the earlier analyses, 146 products approved in both Canada and the United States between 1996 and early 2002 were identified for this study (Table 1). A questionnaire providing each medication's generic and brand names, the name of the manufacturer, the principal indication(s), and the Canadian and US marketing approval dates was sent to six experts chosen on the basis of their knowledge and experience of clinical pharmacology, including that with evaluating drugs for inclusion in formularies or preferred drug lists. Five of the pharmacologists responded; three based in Canada and two in the United States.

Each expert has an extensive knowledge of broad-based clinical pharmacology and many years of experience in the field and is heavily involved in medical education. All the experts have a special focus on optimal and safe use of therapeutic drugs. In addition, they have interests in women's health (2), pharmacoepidemiology and pharmacoeconomics (2), pediatrics (1), diuretics and renal function (1), and anti-arrhythmic drugs and medications that can produce anti-arrhythmias as an adverse effect (1). The experts have served in senior roles in local, provincial/state, national and international organizations and governmental bodies to further optimal and safe medication use, are active leaders within North American learned societies of clinical pharmacology and therapeutics, and have authored numerous important articles and books on clinical pharmacology and therapeutics.

The pharmacologists were requested to categorize the clinical significance of each medication over existing therapy as high, moderate or minimal. These categories were subsequently coded as 1, 2, and 3, respectively. Consideration was given to a finer scale, but categorization beyond three points was thought likely to be overly burdensome for the experts and not necessarily provide more useful results. In addition, they were asked whether the product was of sufficient importance to have received a priority review; their responses were coded 1 for "yes" and 0 for "no." In deciding whether a medication was suitable for priority status, the experts were asked especially to consider the incidence of the disease being treated and the severity of the prognosis, the availability