

Pharmaceutical product discontinuations unrelated to safety

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SYNOPSIS

Safety concerns are not the only reason a drug is withdrawn from the market. Other reasons include product portfolio rationalisation, treatment advances, regulatory reviews of efficacy and demands to reformulate products. Government policies on reimbursement can also lead to withdrawals. More rarely, medicolegal issues can result in discontinuation.

Index words: drug industry, cost of drugs, drug regulation.

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Introduction

Current estimates of the costs of developing a new chemical entity are of the order of US\$600 million spread over approximately 10 years. Worldwide, only one in three products is likely to gain a return on the development costs. Despite this investment a product is sometimes removed from the market for reasons other than safety considerations. While health professionals are usually well informed about drug withdrawals in response to adverse effects, the reasons for other withdrawals may be unclear.

Rationalisation of product portfolios

A successful pharmaceutical research company continuously adds products to the market-place and thus will have an increasing range of products and presentations. The medical need for, and commercial viability of, an increasing portfolio should be reviewed on a regular basis. This may lead to the discontinuation of some presentations or products. Such decisions are not taken lightly. A basis for a decision to discontinue has been described.¹ This process takes into account the need to continue to provide products which meet a specific medical need but which are not commercially viable.

As more pharmaceutical companies amalgamate, reviews of product portfolios become more likely. A newly-merged company will almost certainly increase the range of its product portfolio, but will also create product overlaps. As a result, some products may be discontinued. Since such decisions may come long after the 'hype' of the merger announcement, the cause and effect may not be recognised.

Reviews

The thalidomide tragedy led to the regulation of pharmaceuticals in many Western countries in the late 1960s

or early 1970s. In general, products on the market at the time regulations came into effect received 'grandfather' status. As a result, claims and formulations available at the time were accepted without review. However, in Europe, committees were established to review 'grandfathered' pharmaceutical products. The Committee of Review of Medicines was established in the U.K. in 1975. Companies were required to submit data to support claims for marketed products. As a result, by the end of 1976, approximately 10 000 licences were voluntarily surrendered and other products were discontinued.²

In the European Union, products are now licensed for five years, after which time a renewal is required. While this provides a mechanism for product discontinuations, there is no list of products that may have been discontinued due to this process.

Advances in treatment

Improved treatments may lead to product discontinuations. Mercurial diuretics for the treatment of hypertension were an advance in their day, but their use would now be unacceptable.

New technologies may also lead to product discontinuations. Examples include the plastic ampoules which have replaced some glass vials and facilitated the discontinuation of multidose vials. Product discontinuations may therefore be driven by declining medical need, which in turn is the result of better alternatives.

Formulation changes

Occasionally, the need to reformulate a product results in a review of the value of the product versus the costs of introducing the change. The requirement to replace chlorofluorocarbons (CFCs) with hydrofluoroalkanes (HFAs) as propellants in pressurised metered-dose inhalers is one such example. Agreements to share toxicology data on HFAs reduced the development costs. However, significant resources and expertise are still required to develop the valve technology and document the clinical equivalence between the current CFC products and new HFA products. Smaller companies may decide to discontinue their CFC products rather than incur the costs of developing a replacement containing an HFA.

The European Commission has directed that, in the case of essential substances, once there are at least two HFA alternatives on the market, older formulations of those substances containing CFCs must be withdrawn.

Pharmaceutical reimbursement policies

This is an area of growing controversy as countries implement policies ranging from a free-market approach to restricted lists and reference pricing of subsidised medicines. With the possible exception of the free-market approach, most of the remaining policies have cost containment as their primary goal. However, since pharmaceuticals account for only approximately 10% of most developed countries' health budgets, the maximum cost saving is small compared to what could be achieved in other areas. Furthermore, appropriate pharmaceutical intervention in many cases saves costs in other areas of health expenditure. It is unfortunate that the structure of health funding in Australia and some other countries does not take into account such savings.³

In a review of measures to control the pharmaceutical industry⁴, the authors concluded that price regulation is a relatively crude way of controlling expenditure on pharmaceuticals. The reviewers recognised the Australian efforts to utilise economic analyses to aid the decisions about subsidising new products. However, they also commented that a rigorous evaluation of the impact of the Australian approach is required. Since this review, the Australian government has introduced reference pricing for a number of drug classes. This questions the role of pharmacoeconomic analyses and has the secondary effect of undermining the patent life of new compounds in the affected classes. Such changes may prompt companies to withdraw products or rationalise their product range. In New Zealand, the cost-containment strategies of the drug subsidy agency contributed to the withdrawal of famciclovir and valaciclovir.⁵

Therapeutic best practice

Many countries are developing strategies to ensure patients receive rational drug therapies. Examples include the National Prescribing Service in Australia and the National Institute for Clinical Excellence in the U.K. It is too soon to determine whether or not these schemes will result in product withdrawals. However, in this context, a more active 'delicensing' process has been proposed for the U.K.⁶ Along similar lines, one form of propranolol was discontinued in Japan apparently because of new criteria on clinical usefulness.

Apparent removal

On occasions, a company may decide to license a product to another company. As part of this process, the product name may be changed making it appear that the product has been discontinued.

Medicolegal issues

In some countries, there is a growing move to take legal action if a pharmaceutical product is claimed to have resulted in an undesirable outcome. The *cause celebre* in this regard was Debendox (Bendectin). Some claimed that Debendox was teratogenic. In 1983, the company discontinued the product

because it was not prepared to continue a succession of legal cases in the U.S.A. This decision was taken despite the fact that there was no conclusive evidence that the product was a teratogen.⁷

Information on discontinuations

In Australia deletions from the Pharmaceutical Benefits Scheme are listed in each edition of the Pharmaceutical Benefits Schedule. However, there is no clarifying information about the reasons for withdrawal, some of which could be related to safety.

A complete listing of all products that have been discontinued is available on the Drugdex database, but this also does not include the reasons for discontinuation. The Food and Drug Administration in the U.S.A. requires pharmaceutical companies to notify the administration within 15 working days of discontinuing sale of a product. However, stating the reason for discontinuation is voluntary. While there are a number of possible reasons for product discontinuations, the relative importance of each of these cannot be assessed because there is not enough information to analyse.

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Self-test questions

The following statements are either true or false (answers on page 151)

3. Drugs are only removed from the Australian market if there are safety concerns.
4. When a drug is withdrawn overseas it is automatically removed from the Australian market.