Securing the supply chain

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Summary

Medicines are distributed through a complex supply chain which may be disrupted anywhere from manufacturing to dispensing. Factors that contribute to unanticipated shortages of medicines include manufacturing causes, logistical failures and unexpected or unpredictable disease outbreaks. Additionally, in the postmarketing environment unexpected safety signals may require recall of batches, with a consequential scarcity of remaining supplies at short notice. Early identification of potential stock shortages and early engagement with the Therapeutic Goods Administration will facilitate a coordinated response in managing interruptions or changes to patient care. Pharmaceutical companies and the Therapeutic Goods Administration will endeavour to provide the right product or appropriate alternative therapies to ensure that patient care is not appreciably diminished.

Introduction

The National Medicines Policy has four central objectives focused on delivering medication and related health services that meet best possible health and economic objectives.[1] These objectives are:

- timely access to the medicines that Australians need, at a cost individuals and the community can afford
- medicines meeting appropriate standards of quality, safety and efficacy
- quality use of medicines
- maintaining a responsible and viable medicines industry.

Ensuring timely access to medicines encompasses the entire journey from molecule to patient. It includes research and development programs, a rigorous regulatory system for assessing quality, safety and efficacy,[2] and a government subsidy scheme.[3]

There have been a few notable unexpected shortages in the supply of prescription medicines in Australia. While these events are generally few and far between, when they occur they generate concern and incredulity at the vulnerability of the medicines supply chain.

The supply chain

Medicines are distributed through a complex supply chain starting with formulation and manufacturing. After packaging and labelling, the medicines go to wholesalers and then to pharmacies for dispensing. Within this supply chain there may be international customs and importation hurdles, complex transport needs and a number of rigorous regulatory requirements.

Sponsors of prescription medicines in Australia are typically global companies supplying their drugs to worldwide markets. Determining the quantities which each country requires is largely calculated from historical usage information, recurrent ordering practices and forecasting methods. Intermittent variations in demand and supply may be envisaged and ameliorated, but occasionally this is not the case. Forecasting methodologies are susceptible to numerous variations. These may result in shortages of medicines that are difficult to predict and, at times, impossible to counteract.

Interruptions to supply

Supply may be restricted or delayed anywhere in the supply chain from manufacturing to the dispensary. While sponsors are reliant on accurate forecasting to establish supply requirements, they also depend on successful production. Factors that contribute to unanticipated shortages in medicines supply include manufacturing problems, logistical failures, and unexpected or unpredictable outbreaks of disease. After marketing, unexpected safety concerns may require batches or products to be recalled at short notice. This results in shortages of remaining supplies or of alternative treatment options.

Manufacturing

The causes of production failures can be diverse. Changes in manufacturing processes can cause challenges in meeting regulatory requirements. This is a particular problem with biological products where apparently minor manufacturing changes may create unexpected variations in the quality of the final product.

Many manufacturers rely on third parties for raw materials. If supplies are not received or raw materials fail to meet the required specifications this will disrupt production schedules.

Other examples of production failure include equipment malfunction at factories, finished products not meeting specifications and packaging component failures. Such nonconformities detected during manufacturing processes may lead to losses of whole batches from production with consequent delays in making adequate quantities of the final product available.

Logistics

Non-manufacturing causes may include logistical support failures. For example, inadequate refrigeration during transportation may render a cold chain product unusable. The eruption of an Icelandic volcano in 2010 caused widespread interruption to the transport of air freight. Fortunately, available reserves in Australia meant there were no shortages reported although some safety stocks were drawn upon. Other unanticipated incidents, such as the terrorist attacks on 11 September 2001, caused global disruptions to transportation. Local events such as strikes, although likely to be short-lived, may also disrupt supply channels. The floods in Queensland in January 2011 damaged a pharmaceutical distribution centre, but supplies were obtained from other centres.

Demand

Unexpected increases in demand may occur due to sudden unavailability, or restrictions to the indications, of competitor products. Unexpected disease outbreaks, such as influenza pandemics, also stretch supply. Overcoming shortages or demand surges is particularly challenging if the product lead times are long, as with products manufactured by biotechnology. An example may be that a major supplier of one brand of a multi-brand product becomes unable to supply its product. The unexpected increase in demand for the remaining brands may cause shortages which could take some time to overcome while schedules are altered and manufacturing quantities increased. The planning of manufacturing schedules requires relatively long lead times, therefore unplanned stockpiling of products, for instance, by governments or pharmacies could adversely impact on supply in other regions.

Maintaining supply

The industry's predictive mechanisms do not generally account for unforeseen surges in demand, or for unintended breakdowns in supply. However, extended shelf lives, careful adherence to storage recommendations and maintenance of a reserve stock may compensate for short-lived, unexpected incidents.

There is a fine balance between the holding of safety stock to cover potential shortages and keeping inventory as low as is practicable to avoid wastage caused by stock expiring. As soon as the likelihood of a shortage is confirmed, companies endeavour to establish its probable duration. This will enable the company to determine if safety stocks are sufficient or whether the product can be supplemented from alternative sources.

Vaccines have their own specific challenges and continuation of supply is a constant concern due to the complexity of the production process. Demand is also variable, for example with the uptake of seasonal vaccines. This requires careful stock management and mechanisms for rapid redirection of international supplies.

Sponsors may implement systems whereby stock is assigned and packaged for particular countries at the last minute to enable redirection of supplies at short notice to areas of need. This is a common means of managing the drugs used in clinical trials where recruitment rates may be uncertain.

Cooperation with regulators

When a product is predicted to be out of stock for only a short time, the wholesaler is informed. However, if the shortage is likely to affect the availability of the product to the public, then the Therapeutic Goods Administration (TGA) and Pharmaceutical Benefits Division of the Department of Health and Ageing are advised and a collaborative response is established where necessary. It is a condition of listing on the Pharmaceutical Benefits Scheme (PBS) that sponsors have stock available. They must report any problems that will affect supply of a listed product. There is no requirement for companies to ensure supplies of drugs which are not listed on the PBS.

Under existing exemption mechanisms within the *Therapeutic Goods Act 1989*, pharmaceutical companies may apply to access medicines from alternative sources to cover product shortages. For example, international versions of a product in other strengths, doses or dosage forms, or supplies approved and packaged for countries other than Australia (with non-Australian labelling) may be granted an exemption to enable supply in Australia.[4]

The time needed to resolve the regulatory requirements for alternative supplies can be prolonged. It is therefore imperative for companies to establish transparent and early communication with the TGA in the event of supply problems when expedited assessment of exemption applications may be desired. Similarly, communication within the company, with wholesalers and customers needs to be clear and timely.

In many cases supply problems are resolved without difficulties so widespread notification of potential shortages may be premature. However, prompt notification to the TGA will facilitate a coordinated response to localised or widespread shortages. There are examples where the TGA stipulates that relevant clinicians, colleges, professional bodies and applicable consumer groups are notified of a potential shortage and advised of the proposed contingency strategies. Wider publication of these issues is beneficial when clearly in the

public interest and may be recommended by the Department of Health and Ageing.

In 2008, recalls of batches of heparin-based products led to widespread shortages. The response to this scarcity was closely coordinated between the Department of Health and Ageing and the manufacturers of the affected products. Consensus guidelines for Australian clinicians were developed to provide advice on the use of anticoagulants during the shortage. Substitute treatment regimens with alternative products were established which prioritised patients according to clinical need.[5]

In 2009 supplies of imiglucerase for the treatment of Gaucher's disease, and agalsidase-beta for the treatment of Fabry's disease were significantly depleted due to manufacturing problems. This resulted in a worldwide shortage of these products. The coordinated global and local response recommended rationing the use of remaining product to extend existing supplies for as long as possible.[6] The manufacturer of these products continues to work with government and patient support organisations for the ongoing management of supply.[6]

Conclusion

Medicines manufacturers and suppliers try to prevent shortages of products wherever possible. To achieve this effectively they rely on accurate forecasting, maintenance of appropriate levels of safety-stock and identification of backup supply routes. The TGA has a number of powers under the Therapeutic Goods Act, to permit supply of unapproved products in critical situations.[4]

Early identification of potential stock shortages and early engagement with the TGA enables a coordinated response to assist in managing interruptions or changes to patient care. Both the companies and the TGA will endeavour to provide a product, or appropriate alternative therapies, to ensure that patient care is not appreciably diminished.
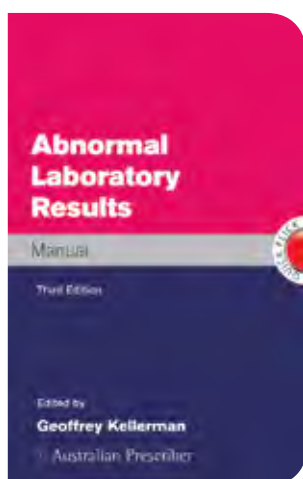
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