The Future of Medical Products
Regulation: How Can Innovation be Safeguarded?

Would less regulation improve innovation in medicines? John Lisman suggests there are lessons to be learned from the medical devices sector.

Innovation in the field of medical products serves both economic and public health interests. The regulatory systems for medical products – whether medicines, medical devices or specific therapies such as cell and gene therapy and tissue engineering – have an impact on innovation and, therefore, on the products which are available to treat patients. Problems with respect to innovation, or rather the lack of it, have been widely identified in numerous publications over the years. This article looks at the differences between the various regulatory systems for medical products and the effects these differences have on innovation and, therefore, the availability of innovative and important therapies. Intellectual property rights, such as patents, deserve specific attention where they represent an important driver for innovation, as well as for national and intergovernmental pharmaceutical policies such as pricing and reimbursement policies.

Medicinal products and medical devices

There are many differences between medical devices and medicinal products. One of the most obvious differences is the way they are used. Medicinal products typically interact directly with patients, while medical devices interact with patients through the healthcare professional. Another important feature is the wide range of products to be defined as medicinal product or medical device.

Essentially, there are only two types of medicinal product: either a small molecule pharmaceutical, usually synthesised chemically, or a biological, such as a protein or a peptide, produced using biotechnology. Within those two types, differences are limited. The medicinal products group consists of around 3,000 active substances. On the other hand, the medical devices category consists of an estimated 10,000 types of products, ranging from sticking plasters, condoms and surgical instruments through implantable devices such as pacemakers and heart valves to diagnostic devices like computerised imaging instruments.

Furthermore, innovation has completely different characteristics for medicinal products and medical devices. For medical devices, innovation is continuous and based on new science, technology and the availability of new materials; because of these continual incremental improvements, they have a short life cycle. European medtech industry association Eucomed mentions an average of 18 months – this would be the time from marketing a medical device until its replacement reaches the market. Moreover, the drive for new developments is often user-related. The pharmaceutical industry, by contrast, innovates through finding new active substances for use in medicinal products. The development time for a new medicinal product is long, as is the product life cycle. The differences between the two groups are reflected in the systems regulating their access to market.

Market access for medicinal products

Market access for medicinal products depends on premarketing authorisation of the product and the labelling. Pharmaceutical legislation in all (developed) regions of the world is based on testing the (chemical-pharmaceutical) quality, safety and efficacy of the product. The European Union implemented pharmaceutical regulation in 1965, soon after the thalidomide tragedy occurred, although national systems for the testing of industrially prepared pharmaceuticals existed before. At that time the US already had a rudimentary regulatory system.

The first regulatory systems were mainly directed at ensuring the quality of medicinal products. After the thalidomide crisis, the focus shifted to the safety aspects of new compounds, and from 1975 attention turned to proof of efficacy through clinical trials. This trend led to an increase in the development time for a new medicinal product as well as a steep rise in development costs. During the past decade the trend has returned to safety because of unexpected safety problems such as those with Vioxx (rofecoxib), which was withdrawn from the market in 2004 due to suspected cardiovascular adverse events, and Baycol/Lipobay (cerivastatin), which was withdrawn in 2001 because of severe adverse effects.

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Medicinal products and innovation

The main driver for innovation in the life science industry is of a financial nature and relates to return on investment. An important factor in the area of medicinal products is generic competition: if a product is off-patent, a copy product can be authorised and compete with respect to price and market share with the originator product. The innovative pharmaceutical industry would not innovate if patent protection was not available. In other words, the pharmaceutical industry paradigm is pointing in one direction: develop a drug in an exclusive market (with patent protection) and sell it at the highest possible price. Developing a new medicinal product takes between ten and 15 years and is extremely expensive – a figure of around $1 billion has been suggested.

Those two factors (time and cost) are important because they affect the level of innovation. The high costs of developing a new medicine are directly related to the dossier requirements for market access and there is concern that the current costs of drug development are unsustainable. Raising the funds necessary for the development of a new drug is only possible for big companies. Even if the development of a product is successful in terms of its safety and efficacy, it is important that society can afford, and will choose, to use it. Another aspect of the huge cost of drug development is the fact that new products need to generate annual sales of about $500 million to be able to recoup the cost of development. This has implications for the size of the market in terms of patients, because prices have their natural limits. The high costs of development steer companies towards the search for blockbuster drugs only: medicinal products for huge populations, to be used life-long.

From an economics perspective this is all quite logical, but the public health effects of this mechanism are not always perfect. Obvious examples of lack of market incentives are orphan drugs and medicines for children. As orphan drugs are intended for rare diseases, normal market forces do not offer enough incentive to develop them, and specific legislation has been implemented to do so: the US Orphan Drug Act of 1983 and EU Regulation (EC) No 141/2000. Fortunately, only few children are ill, but those who are must be treated with medicines tested specifically in children. This is also an area where not enough market incentive exists, although in this area too specific paediatric medicines legislation has been implemented in the US and the EU with both obligations and rewards for the pharmaceutical industry.

A third category of products that are not spontaneously developed is medicines for so-called “neglected diseases” such as tropical diseases that cause an enormous health burden, but mainly outside the developed world.

Pharmaceutical companies look after their products as long as they have the exclusive rights, but as soon as patents expire, a medicinal product will get orphaned: new applications of an active substance are not developed, because no one feels responsible for the product. The consequence of this is that many medicinal products are used off-label – a practice that could account for as much as 50% of the actual use of a particular medicinal product. A company planning to develop a new indication for a medicinal product has to consider the profit this would create. For older products, no patent protection is available, so the investment would not pay off. Other reasons not to develop an off-label use could be of a legal or practical nature: if a product is not authorised for an indication or population, this might limit liability for adverse events.

Market access of medical devices

Medical devices are regulated differently from medicinal products: the evaluation of the latter is directed at quality, safety and efficacy, while for medical devices market access is regulated mainly through risk management systems. The main difference in the development of the two types of product is that the authorisation of a medicinal product requires extensive clinical testing, while for devices mechanical performance in laboratory tests is often sufficient. The regulatory systems for medical devices are more recent than those for medicinal products: medical devices regulation started in the EU in 1990, when medicinal products regulation already had a 25-year history.

In the EU, a premarketing approval for medical devices will be given by the company itself (for very low-risk products such as sticking plasters) or by a notified body, not by a governmental agency (in the US medical devices are regulated under the Federal Food, Drug, and Cosmetics Act). Generally, the notified body evaluates the device dossier to see if it meets the essential requirements. If it does, a CE mark can be attached to the product. After marketing, a vigilance system to monitor adverse events such as device failure has to be put in place.

Medical devices and innovation

In 2000, the European Commission commissioned a study of the impact of medical devices legislation. An important aspect was the degree of innovation in the sector, and how this could
be considered to be influenced by the regulatory system. In the years under review, the medical device sector did quite well in terms of growth rate and performance on the stock market. In 2003, the functioning of the regulatory system for medical devices was evaluated as a consequence of a provision in the main medical device directive, Directive 93/42/EEC.9

On the basis of this evaluation, a proposal for the review of the legislation was drafted. The conclusions were quite positive: both the European Commission and the users of the legislation were satisfied. The medical devices sector is growing fast and is very innovative. Fast market access and regulation by parties in the marketplace (ie the notified bodies) leads to short-term competition among manufacturers, based on incremental innovation. In the medical device sector, developing blockbuster products is less of a goal than for medicinal products. It also became clear that the share of turnover being invested in marketing in the devices sector lagged behind that in the pharmaceutical sector. In the meantime, the revision of the medical devices legislation was completed in September 2007.

The different regulatory systems and innovation

The regulatory system and innovative characteristics of medicinal products and medical devices differ extensively. The most important difference with respect to regulatory aspects seems to be the level of the dossier requirements. For medicinal products the requirements, especially with respect to clinical testing, are very high and have grown very sharply. For medical devices the dossier requirements are much lower. Clinical trials are only necessary in exceptional cases where warranted by safety and efficacy concerns.

As a consequence, the development of medicinal products is much more time-consuming and much more expensive than the development of medical devices. The high cost of developing a medicinal product results in a number of factors which are unfavourable for innovation. The pharmaceutical industry can only recover its R&D costs by the availability of a big, exclusive market and by maintaining a long product life cycle. To create a big market, treatments are developed for large populations and for long treatment periods (preferably lifetime). To keep exclusivity, the medicinal product in question needs to be protected extensively with intellectual property rights (mainly patents).

Because of the less rigorous premarketing requirements for a medical device, the costs of R&D are much lower. Moreover, the product life cycles for medical devices are much shorter. Companies manufacturing medical devices do not have to rely on one or two blockbusters for their profits, and can either be smaller or be present on more than one of the smaller markets. There is less focus on protecting inventions, and the market with respect to licences and patents is more or less comparable to other industry sectors. Development and innovation are less restrained by regulation than in the medicinal products sector.

How to promote innovation?

The greater the requirements of the regulatory system, the higher the cost of development and the longer the product development time. For medical devices, the current situation is beneficial for innovation. However, there is already a trend towards introducing clinical trials into the development of medical devices. The reasons for this are mainly in the area of reimbursement and pricing; even though a medical device functions well, it is still important to evaluate its cost-effectiveness compared with other available treatments. The most important source of information for this type of evaluation is head-to-head comparisons in clinical trials.

With respect to the evaluation of medicinal products, there are suggestions that regulatory authorities are becoming more risk-averse than necessary, and that more flexibility in their approach is necessary.10

This leads me to the suggestion that a meta-analysis of the dossier requirements for medical products is needed. As there is a direct relation between the cost of product development and the level of innovation, an imbalance could be created by asking for too much information, especially if the necessary data have to be gathered by performing expensive clinical trials. Any new requirement for trials and studies in the development of medical products would have to be weighed on the balance of "need to know" and "nice to know", while bearing in mind that to be on the safe side could mean a serious hurdle for innovation. If innovation stagnates, the patient care of the future is jeopardised, because new products will not become available.

Conclusion

Which medical products do we get, and which will we have in 20 years’ time? The products that come out of R&D meet both scientific and regulatory criteria, which are the outcome of policy and legislation, and the economic criteria of the market.
As far as the regulatory systems are concerned, that for medical devices seems to perform better in terms of innovation than the pharmaceutical system. The main reason for this could be the fact that development costs resulting from dossier requirements are lower for medical devices than for medicinal products. As a consequence, there is less focus on intellectual property rights and long product life cycles in the medical devices sector than in pharmaceuticals. What needs to be done about this?

One step that could prove very useful would be the development of a strategy of deregulation of the marketing authorisation process. To start this process, a risk-benefit analysis of the regulatory systems should be conducted. In this analysis, alternative methods of gathering information about the balance would be used. To compensate for the societal risk of a lighter approval system for medicinal products, there could be a greater focus on (regulatory) risk management. And finally, (future) medical needs should be acknowledged as drivers for innovation. Currently, economic factors decide on the development of medical products and medical devices. The paradoxical situation has arisen where those who pay for medicinal products—governments, social security systems and insurers and patients—have no influence at all on the treatments that will be available in the future when we need them.

References
1. Eucomed website, www.eucomed.org