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Extensions of indication throughout the drug product lifecycle: a quantitative analysis

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The marketing authorisation of the first generic product version is an important moment in a drug product lifecycle. The subsequently changed intellectual property protection prospects could affect the incentives for further drug development. We assessed the quantity and nature of extensions of indication of small molecule medicinal products authorised through the European Medicines Agency throughout the drug product lifecycle with special attention for the impact of the introduction of a first generic competitor. The majority (92.5%) of the extensions of indication was approved during the exclusivity period of the innovator product. Regulatory rethinking might be needed for a sustainable stimulation of extensions of indications in the post-generic period of a drug product lifecycle.

Problem statement

Q2 A crucial issue of drug development strategies is the time horizon for innovator pharmaceutical companies to recoup their investments. To increase the probability of a sufficient return on investment, innovations can be protected from competitors by patents and other exclusivity rights (e.g. data exclusivity) [1]. This creates a period of market exclusivity, during which pharmaceutical companies are essentially the sole manufacturer of a product [2].

During the period of market exclusivity, pharmaceutical companies can increase the usage potential of their products, and thereby return on investment, by extending the therapeutic indication of their products [3]. Once the drug product is proven to be effective and safe for the new indication, it can be included in the marketing authorisation (i.e. the label) of the drug. More indications in the label enlarge the patient population that could use the drug; which in turn increases sales. Moreover, the market exclusivity period can be extended if a new indication is added to the label. For example, in the EU an additional year of data exclusivity can be awarded if a drug is approved for one or more new therapeutic indications that bring a significant clinical benefit in comparison with existing therapies [4].

Previously, Grabowski *et al.* showed that in the USA innovator products have on average a period of market exclusivity of 12.9 years [5]. During the market exclusivity period it is common practice for pharmaceutical companies to continue clinical trials in search for marketing authorisation, and to add new indications [6,7]. DiMasi demonstrated that 982 new use approvals were authorised between 1998 and 2011 for drugs authorised in the USA, including new indications and new populations [8]. In the EU the number of applications for extensions of indication is about the same as the number of applications for new medicinal products [9]. Overall, the development of new indications accounts for a substantial share of pharmaceutical innovation.

Upon expiration of patents and other exclusivity rights of the innovator product, generic products enter the market. Consequently, the market share of the innovator product plummets [5,10]. From the perspective of public health and cost-containment cheaper alternatives become available for clinical use

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[11,12]. However, patent expiration and generic competition can have major consequences for investments in further studying and regulatory processing of new, additional indications. Innovator companies will benefit less from extensions of the indication after the approval of a generic competitor than during the initial market exclusivity period. Although new patents and regulatory protection can be obtained for an extension of indication, current clinical practice shows frequent prescribing of generic medicinal products for the extended indications, even though the generic product versions are not authorised for these new therapeutic indications. Moreover, once a patent has been obtained it can be challenged by other pharmaceutical companies – with an uncertain outcome. Likewise, generic companies can study and apply for extensions of indication for their products, but they face the same problem regarding lack of incentives as innovator companies. All this sounds logical but so far the issue: to what extent new indications are developed once generic products are approved, has been poorly studied.

In this analysis, we determined the quantity and nature of extensions of indication of small molecule medicinal products authorised through the European Medicines Agency (EMA). Subsequently, we compared the frequency of extensions of indication throughout the drug product lifecycle with special attention for the impact of the authorisation of the first generic product per active substance. We hypothesised that neither indications of innovator products nor generic products were extended around the time of introduction of the first generic product version.

Approach

A list of small molecule medicinal products authorised since the beginning of the EU centralised procedure, or authorised and later withdrawn, up to 31 August 2013 was obtained from the EMA website (http://www.ema.europa.eu/ema/). Subsequently, the medicinal products with active substances first authorised in Europe through the EMA were selected. These were grouped by active substance in which different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives were considered as the same active substances. Combination products constituted their own 'active substance'. The active substances were our unit of analysis.

For each active substance, the duration of the 'innovator period' and the 'generic period' was calculated. The innovator period was defined as the time between the marketing authorisation of the first innovator product and the first generic product. The approval of the first generic product marks the expiration of patents and other exclusivity rights on the active substance. The generic period comprised the time between the marketing authorisation of the first generic product and 31 August 2013; the date on which data collection started. Active substances were eligible for analysis, if the generic period lasted at least one year, because it was assumed that these needed at least this period of time to obtain approval for a new indication.

Subsequently, the European Public Assessment Report (EPAR) of each medicinal product was collected from the EMA website. This document contains references to changes of the marketing authorisation (e.g. extensions of indication). In addition, the initial Summary of Product Characteristics (SmPCs) and its subsequent versions were collected from the Pharmaceuticals Community Register of the European Commission (http://ec.europa.eu/health/documents/community-register/) if the SmPCs were necessary to characterise the nature of the extensions of indication.

Per active substance, the EPARs were screened for references to 'extensions of indication'. The approval dates of the extensions of indication were extracted from the EPARs. In addition, initial indications of subsequent products per active substance were considered as extension of indication. For instance, the approval of Aclasta (zoledronic acid) for the treatment of Paget's disease was regarded an extension of indication, because Zometa® (also zoledronic acid) was only authorised for prevention of skeletal-related events and the treatment of tumour-induced hypercalcaemia [13,14]. Extensions of indication were only counted the first time an indication was approved per active substance.

The active substances, medicinal products, marketing authorisation dates and extensions of indication – including the approval dates – were entered into a database. The number of extensions of indication per year was plotted with a distinction between the innovator period and the generic period. In this graph $t = 0$ is the marketing authorisation date of the first generic product per active substance. The rate of extensions of indication in the innovator period and generic period were calculated.

New indications

In total, we identified 557 small molecule medicinal products that were approved in Europe through the centralised procedure and that were authorised or withdrawn up to 31 August 2013. The medicinal products included 297 different active substances or combinations of active substances. Of these, 26 met the subsequent selection criteria of approval of one or more generic products with a follow-up period of at least one year. These 26 active substances comprised 186 products: 65 innovator products and 121 generic products (Table 1). The innovator products were first authorised between 1995 and 2001. The generic products were authorised between 2007 and 2012. The median number of innovator and generic products per active substance was 2 [interquartile range (IQR) 2–4] and 4 (IQR 2–6), respectively. The median length of the innovator period was 11.2 years (IQR 11.0–12.3 years), whereas it was 3.6 years (IQR 2.5–4.1 years) for the generic period.

In the analysis of the 26 active substances, we identified 53 extensions of indication, of which two concerned changes to the posology (i.e. paediatric posology). These all applied to innovator products. Fig. 1 displays the number of extensions of indication per time interval of 3 years before and after the approval of the first generic product. It shows that the vast majority of extensions of indication ($n = 49$; 92.5%) were authorised in the innovator period. The first was authorised on average 5.2 years [standard deviation (Sd) 3.3 years] after approval of the first innovator product and 6.5 years (Sd 3.3 years) before the approval of the first generic product. The incidence of extensions of indications was 49/304.6 years during the innovator period and 4/88.3 years during the generic period. Fig. 1 also displays how the number of extensions of indication accumulates each year. It increases steadily until 3 years before the approval of the first generic product ($t = 0$) when it starts to level off. Subsequently, 2 years after approval of the first generic product version no extensions of indication were identified during the study period.

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