



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

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 European Union (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 the EU 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 (Fig. 1). 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 the EU 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.

In more detail, Fig. 2 depicts the number of extensions of indication per active substance. On average 2.0 (Sd 2.1) extensions

TABLE 1

Active substances included in the analysis of extensions of indication

Active substance	Innovator ^a							Generic ^b		
	ATC group	Brand name	Company	Approval date ^c	Products ^d	Years ^e	Initial scope ^f	Approval date ^g	Years ^h	Products ⁱ
Pioglitazone	A10BG03	Glustin/Actos	Takeda	11-10-2000	2	11.4	Type 2 diabetes	9-3-2012	1.5	8
Repaglinide	A10BX02	NovoNorm/Prandin	Novo Nordisk	17-8-1998	2	10.9	Type 2 diabetes	29-6-2009	4.2	4
Clopidogrel	B01AC04	Clopidogrel BMS/ Plavix/Iscover/ Clopidogrel Zentiva/ Grepid	Bristol-Myers Squibb/Sanofi/ Sanofi-Aventis/ Pharmathen	15-7-1998	4	11.0	Reduction of atherosclerotic events (myocardial infarction, stroke, death due to vascular causes)	21-7-2009	4.1	23
Irbesartan	C09CA04	Irbesartan BMS/ Aprovel/Karvea/ Irbesartan Zentiva	Bristol-Myers Squibb/Sanofi/ Sanofi-Aventis	27-8-1997	4	11.3	Essential hypertension	1-12-2008	4.8	3
Irbesartan/hydrochlorothiazide	C09DA04	Irbesartan Hydrochlorothiazide BMS/CoAprovel/ Karvezide/Irbesartan Hydrochlorothiazide Zentiva	Bristol-Myers Squibb/Sanofi/ Sanofi-Aventis	15-10-1998	4	11.0	Essential hypertension	23-10-2009	3.9	2
Telmisartan	C09CA07	Pritor/Kinzalmono/ Micardis	Bayer/Boehringer Ingelheim	11-12-1998	3	11.1	Essential hypertension	26-1-2010	3.6	4
Raloxifene	G03XC01	Evista/Optruma	Daiichi Sankyo/Eli Lilly	5-8-1998	2	11.7	Non-traumatic vertebral fractures in postmenopausal women	29-4-2010	3.3	1
Sildenafil	G04BE03	Viagra/Patrex/ Revatio	Pfizer	14-9-1998	3	11.0	Erectile dysfunction	21-9-2009	3.9	4
Efavirenz	J05AG03	Stocrin/Sustiva	MSD/Bristol- Myers Squibb	28-5-1999	2	12.6	HIV	9-1-2012	1.6	1
Lamivudine	J05AF05	Epivir/Zeffix	ViiV Healthcare/ Glaxo Group	8-8-1996	2	13.2	HIV	23-10-2009	3.9	2
Lamivudine/zidovudine	J05AR01	Combivir	ViiV Healthcare	18-3-1998	1	13.0	HIV	28-2-2011	2.5	1
Nevirapine	J05AG01	Viramune	Boehringer Ingelheim	5-2-1998	1	11.8	HIV	30-11-2009	3.8	1
Capecitabine	L01BC06	Xeloda	Roche	2-2-2001	1	11.2	Metastatic colorectal cancer	20-4-2012	1.4	5
Docetaxel	L01CD02	Taxotere/Docetaxel Winthrop	Aventis	27-11-1995	2	14.2	Metastatic breast cancer	26-1-2010	3.6	6
Leflunomide	L04AA13	Arava/Leflunomide Winthrop	Sanofi-Aventis	2-9-1999	2	10.9	Active rheumatoid arthritis	27-7-2010	3.1	4
Mycophenolate mofetil	L04AA06	CellCept	Roche	14-2-1996	1	12.0	Prophylaxis of acute transplant rejection	21-2-2008	5.5	3

Temozolomide	L01AX03	Temodal	MSD	26-1-1999	1	11.0	Glioblastoma multiforme	25-1-2010	3.6	6
Topotecan	L01XX17	Hycamtin/Evotopin	SmithKline Beecham/ Beecham Group	12-11-1996	2	12.7	Metastatic carcinoma of the ovary	24-7-2009	4.1	5
Ibandronic acid	M05BA06	Bondronat/Destara/ Bonenza/Bonviva	Roche	25-6-1996	4	14.2	Tumour-induced hypercalcaemia	17-9-2010	3.0	4
Zoledronic acid	M05BA08	Zometa/Aclasta	Novartis	20-3-2001	2	11.1	Tumour-induced hypercalcaemia	20-4-2012	1.4	6
Entacapone	N04BX02	Comtess/Comtan/ Entacapone Orion	Orion Corporation/ Novartis	16-9-1998	3	12.4	Parkinson's disease	18-2-2011	2.5	1
Levetiracetam	N03AX14	Keppra	UCB Pharma SA	29-9-2000	1	10.9	Epilepsy	26-8-2011	2.0	7
Olanzapine	N05AH03	Zyprexa/Olansek/ Zyprexa Velotab/ Zypadhera	Eli Lilly	27-9-1996	4	11.0	Schizophrenia	27-9-2007	5.9	9
Pramipexole	N04BC05	Sifrol/Daquiran/ Mirapexin	Boehringer Ingelheim/Dr. Karl Thomae	14-10-1997	3	10.9	Idiopathic Parkinson's disease	12-9-2008	5.0	3
Rivastigmine	N06DA03	Exelon/Prometax/ Rivastigmine Hexal/ Rivastigmine Sandoz	Novartis/Hexal/ Sandoz	12-5-1998	4	10.9	Alzheimer's dementia	17-4-2009	4.4	4
Desloratadine	R06AX27	Aerius/Allex/ Azomyr/Neoclaritin/ Opulis	MSD/Schering- Plough	15-1-2001	5	10.9	Seasonal allergic rhinitis	24-11-2011	1.8	4

^a The innovator products were defined as the medicinal product that was approved first and all other medicinal products with the same active substance manufactured by the same company, or group of companies (e.g. in a joint marketing or licensing agreement).

^b Generic products were all products not designated as innovator products.

^c Marketing authorisation date of the first innovator product.

^d Number of products considered as innovator products.

^e Length of the innovator period in years.

^f Scope of the indication of the first innovator product.

^g Marketing authorisation date of the first generic product.

^h Length of the generic period in years.

ⁱ Number of products considered as generic products.

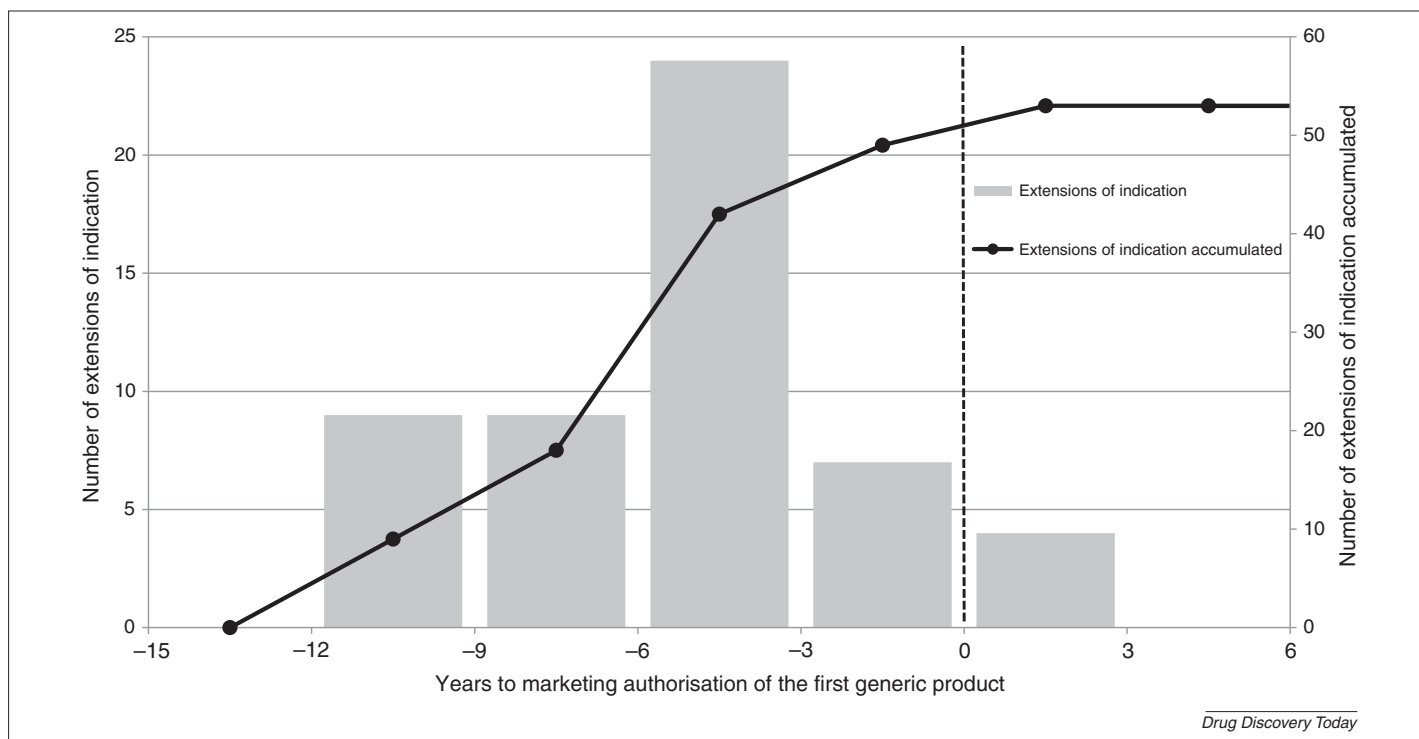


FIGURE 1

Number of extensions of indication synchronised by the marketing authorisation of the first generic product per active substance. Bars indicate the absolute number of extensions of indication (left y axis) relative to the entry of the first generic product version for each active substance, denoted as $t = 0$. The line represents the cumulative number of extensions of indications during the analysis period (right y axis).

of indication were approved per active substance. However, the active substances varied considerably in the number of extensions of indication. Docetaxel had the most extensions of indication ($n = 9$), whereas six active substances had none. The four extensions of indication in the generic period related to four individual active substances.

Dynamics of extensions of indications

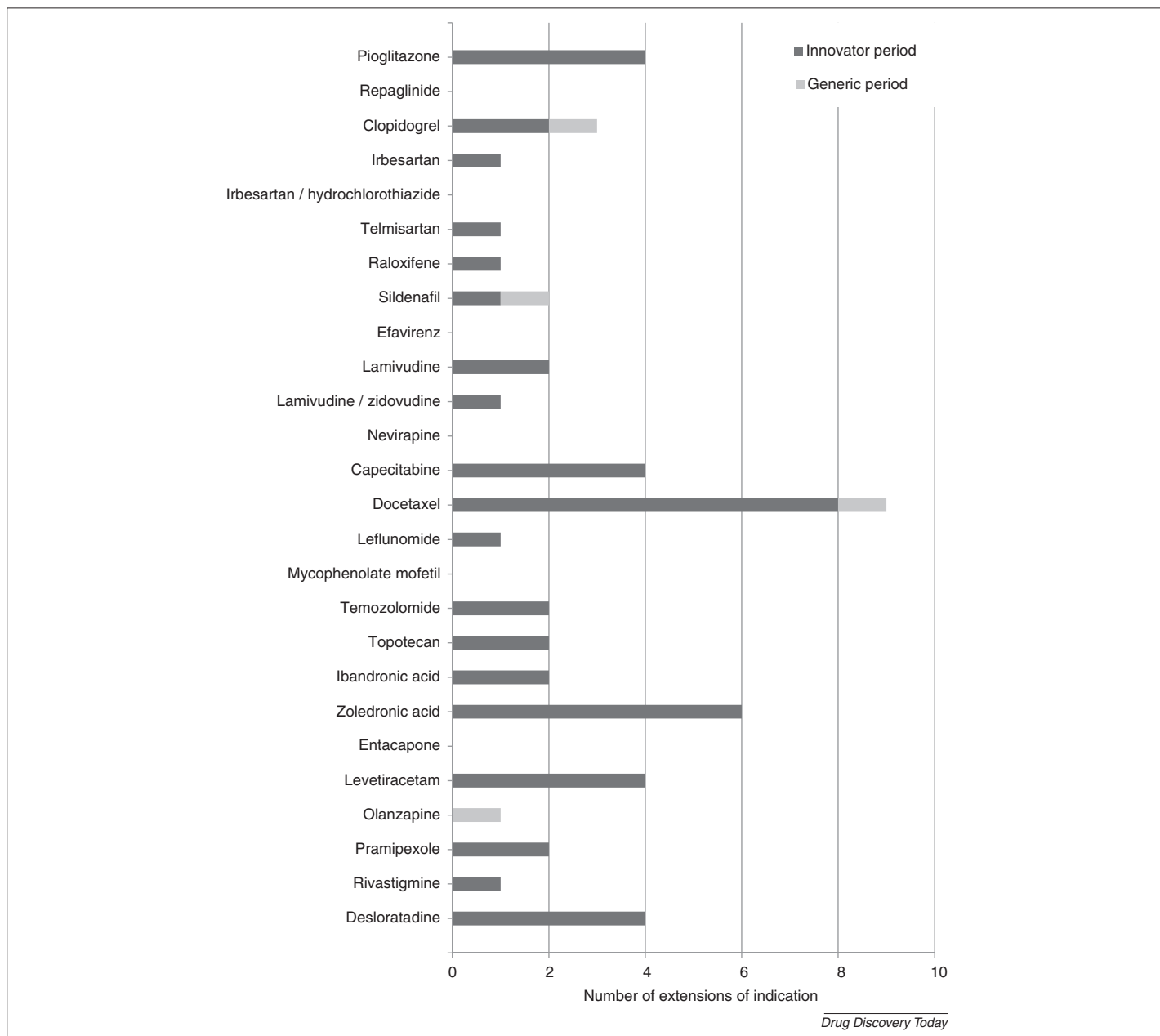
In this analysis, we observed the following dynamics of the extensions of indication in the drug product lifecycle: an upsurge after the initial marketing authorisation, a peak 6 to 3 years before generic introduction and a decline starting ~ 3 years before generic introduction, and no new extensions of indications were observed 2 years thereafter. During the study period extensions of indication were only approved for innovator products and mainly during the innovator period; only shortly after the start of generic competition was a limited number of extensions of indication approved. These results are in line with our hypothesis that the number of extensions of indication ceases around the time a generic product version is approved.

The upsurge and subsequent peak could be the result of pharmaceutical companies seeking to enlarge their market, and it could also provide them with an extension of their market exclusivity period. The incline in extensions of indication started a few years after initial authorisation of the innovator products, which could be explained by the fact that companies would have needed time to complete clinical studies in support of the new indication. Anticipating the introduction of generic competitors the innovator companies might have ceased the development of additional

indications years earlier to that moment. The extensions of indication after generic introduction could generally be explained by a delay in the drug development, for example prolonged clinical development.

In addition, two of the four extensions of indication in the generic period seem to be explainable by the ongoing specific intellectual property protection. Zypadhera® (olanzapine) was authorised as a prolonged-release dosage form for maintenance treatment in schizophrenia therapy. In contrast to Zyprexa® (olanzapine), Zypadhera® contains olanzapine pamoate, which is still under patent protection [15]. For Revatio® (sildenafil) a paediatric indication for the treatment of pulmonary arterial hypertension was approved. Revatio®, but not Viagra®, which has the same active substance, still benefits from 10 years of marketing exclusivity as an orphan drug. The other two extensions of indication in the generic period were for clopidogrel (Plavix®, Iscover®, Clopidogrel Zentiva®) in atrial fibrillation and docetaxel (Taxotere®, Docetaxel Winthrop®) in the treatment of node-negative breast cancer. The clinical trials supporting these extensions of indication might have been performed during the innovator period, whereas the inclusion in the label might have been delayed.

The incidence of extensions of indication has received little attention in literature. In 2006, Berndt *et al.* studied the number of supplemental indications of angiotensin-converting enzyme inhibitors, proton-pump inhibitors/H₂-antagonists and selective serotonin reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors between 1984 and 2004 [3]. For all three groups they found a considerable number of extensions of indication, which

**FIGURE 2**

Total number of extensions of indication per active substance. Dark bars represent extensions of indication during the innovator period and light bars represent extensions of indication during the generic period.

seemed to have been approved mainly during the 12 years after approval of the initial indication. However, they did not relate the extensions of the indication to the approval of generic versions of the products. DiMasi demonstrated a fluctuation in the number of supplemental indications per year between 1999 and 2011 in the USA without exhibiting a marked trend [8].

Length of exclusivity period and scope of the new indications

Our identified 11.2 years of innovator period approximates the average length of the market exclusivity period identified in previous studies [5,16]. However, these periods are noticeably shorter than the 15 years of exclusivity the EU legislator deemed

necessary to cover for the investments in drug development when it established the EU Supplementary Protection Certificate (SPC) [17]. The SPC prolongs the basic patent as compensation for the time between the filing of the patent and the initial marketing authorisation with a maximum of 5 years [18]. The SPC in the EU is similar to the patent term restoration in the USA [2]. The short market exclusivity period could be explained by the soaring drug development time over the years up to 14.2 years for drugs approved in the USA between 1990 and 1999 [19]. More-recent data show that clinical development and regulatory approval ranged from 5.8 years for AIDS antiviral drugs to 8.7 years for antineoplastic drugs approved by the FDA in the period 2003–2007 [20]. This excludes the time involved in discovery and preclinical

testing of the drug. The remaining period of patent protection cannot be extended with the SPC to the aforementioned 15 years.

We noticed that the extensions of indication differed in their respective scopes. Some extensions of indication seemed to be within the scope of the original indication. For instance the therapeutic indication of pioglitazone, an antidiabetic drug, has been extended with variations to the treatment of type 2 diabetes mellitus [21]. Other drugs have been extended with indications outside the scope of their original use. A prime example is sildenafil, which is used for the treatment of erectile dysfunction (Viagra®) [22], and afterwards was authorised for pulmonary hypertension (Revatio®) [23].

Implications for public health

From a public health perspective, it is important that new indications are developed and the results are included in a marketing authorisation and product information. The application for authorisation enables an in-depth benefit:risk assessment by the competent authorities. Moreover, after approval the new indications will be included in the official product information (e.g. the package leaflet). This provides physicians and patients with reliable information about the use of the product, including posology and potential side effects.

A substantial share of the authorised drugs has subsequent indications that are not included in a marketing authorisation, as the commonness of off-label use indicates [24–27]. Radley *et al.* estimated that 21% of the overall medication use is off-label, whereas 73% of those uses were supported by little or no scientific evidence [28]. In addition, many potentially new indications for approved drugs have been suggested based on *in vitro* and *in silico* techniques used for drug repositioning [29]. The fact that our analysis showed that approval of extensions of indication by a regulatory authority mainly occurred during the pre-generic period is of concern from this point of view. The relative absence of extensions of indication in the generic period, despite the presence of potential new indications, could question the capability of the regulatory system to facilitate continuous innovation in the form of extensions of indication. Regulatory rethinking might be needed to overcome some of the obstacles faced in this respect.

In future research it would be interesting to determine whether the decrease in extensions of indication correlates with a reduction in clinical research. Because clinical trials are needed to confirm the efficacy and safety of a drug in new indications, a decrease in clinical trials might precede a reduction in extensions of indication. We focused on the influence of generic competition on the rate of extensions of indication. Another interesting question for future research is how this rate is affected by the authorisation of me-too products (subsequent

products within a therapeutic class), because they also pose competition.

Limitations of the analysis

Several limitations to our analysis should be noted. Firstly, we assessed the first cohort of medicinal products with generic competitors authorised in the European centralised procedure, which has only been in place since 1995. For most of the 297 active substances no generic products are yet authorised. This explains the rather small sample size. Secondly, the centralised procedure is only one of the regulatory routes to obtain a marketing authorisation in the EU. Extensions of indication could be included in marketing authorisations granted through the decentralised procedure or the national procedure. Lastly, we did not have the same follow-up time for each active substance. This differed particularly for the generic period. However, the decline in and subsequent absence of extensions of indication after generic introduction might only be partially attributed to differences in follow-up time of active substances in the generic period. Three, four and five years into the generic period, we had data on 20, 17 and eight active substances, respectively, and no extensions of indication were approved during those years.

Concluding remarks

During the study period innovator products were approved for new indications during their lifecycle, whereas generic products were not. Extensions of indication were mainly authorised a few years before approval of the first generic product version. Regulatory rethinking might be needed for a sustainable stimulation of extensions of indications in the post-generic period of the drug product lifecycle, especially for the sake of public health.

Conflicts of interest

The authors declared no potential conflicts of interest that are directly relevant to the content of this article.

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References

- 1 Higgins, M.J. and Graham, S.J.H. (2009) Intellectual property. Balancing innovation and access: patent challenges tip the scales. *Science* 326, 370–371
- 2 Glover, G.J. (2007) The influence of market exclusivity on drug availability and medical innovations. *AAPS J.* 9, E312–E316
- 3 Berndt, E.R. *et al.* (2006) The impact of incremental innovation in biopharmaceuticals: drug utilisation in original and supplemental indications. *Pharmacoeconomics* 24 (Suppl. 2), 69–86

- 4 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Art. 10, paragraph 5). Available at: <http://eur-lex.europa.eu/>.
- 5 Grabowski, H. *et al.* (2014) Recent trends in brand-name and generic drug competition. *J. Med. Econ.* 17, 207–214
- 6 Sandner, P. and Ziegelbauer, K. (2008) Product-related research: how research can contribute to successful life-cycle management. *Drug Discov. Today* 13, 457–463
- 7 Van Luijn, J.C.F. *et al.* (2011) Post-approval trials of new medicines: widening use or deepening knowledge? Analysis of 10 years of etanercept. *Scand. J. Rheumatol.* 40, 183–191
- 8 DiMasi, J.A. (2013) Innovating by developing new uses of already-approved drugs: trends in the marketing approval of supplemental indications. *Clin. Ther.* 35, 808–818
- 9 Leufkens, H.G.M. *et al.* (2011) Post-innovation innovation of medicinal products. *Drug Discov. Today: Technol.* 8, e1–e42
- 10 Kesselheim, A.S. (2010) Using market-exclusivity incentives to promote pharmaceutical innovation. *N. Engl. J. Med.* 363, 1855–1862
- 11 Van Mourik, M.S.M. *et al.* (2010) Availability, price and affordability of cardiovascular medicines: a comparison across 36 countries using WHO/HAI data. *BMC Cardiovasc. Disord.* 10, 25
- 12 Gumbs, P.D. *et al.* (2007) Society already achieves economic benefits from generic substitution but fails to do the same for therapeutic substitution. *Br. J. Clin. Pharmacol.* 64, 680–685
- 13 Summary of product characteristics Zometa (EMA/H/C/336/II/1). Commission Decision 2856 [2002] OJ C206/3. Available at: http://ec.europa.eu/health/documents/community-register/2002/200207195512/anx_5512_en.pdf.
- 14 Summary of product characteristics Aclasta (EMA/H/C/595), Commission Decision 1246 [2005] OJ C104/15 Available at: http://ec.europa.eu/health/documents/community-register/2005/200504159338/anx_9338_en.pdf.
- 15 Eli Lilly and Company (2005). Olanzapine Pamoate Dihydrate. EP 1838716.
- 16 Seoane-Vazquez, E. *et al.* (2008) Incentives for orphan drug research and development in the United States. *Orphanet J. Rare Dis.* 3, 33
- 17 Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products – Preambles.
- 18 Gassner, U.M. (2014) Recent developments in the area of supplementary protection certificates. *Pharmaceut. Policy Law* 16, 45–72
- 19 Dimasi, J.A. (2001) New drug development in the United States from 1963 to 1999. *Clin. Pharmacol. Ther.* 69, 286–296
- 20 Kaitin, K.I. (2010) Deconstructing the drug development process: the new face of innovation. *Clin. Pharmacol. Ther.* 87, 356–361
- 21 Summary of product characteristics Actos (EMA/H/C/000285/II/23) Commission Decision 312 [2007] OJ C39/7. Available at: http://ec.europa.eu/health/documents/community-register/2007/2007012619688/anx_19688_en.pdf.
- 22 Summary of product characteristics Viagra (EMA/H/C/202) Commission Decision 2645 [1998] OJ C297/2. Available at: http://ec.europa.eu/health/documents/community-register/1998/199809143246/anx_3246_en.pdf.
- 23 Summary of product characteristics Revatio (EMA/H/C/638) Commission Decision 4326 [2005] OJ C293/11. Available at: http://ec.europa.eu/health/documents/community-register/2005/2005102810246/anx_10246_en.pdf.
- 24 Walton, S.M. *et al.* (2008) Prioritizing future research on off-label prescribing: results of a quantitative evaluation. *Pharmacotherapy* 28, 1443–1452
- 25 Gijzen, R. *et al.* (2009) Frequency of ill-founded off-label prescribing in Dutch general practice. *Pharmacoepidemiol. Drug Saf.* 18, 84–91
- 26 Cras, A. *et al.* (2007) Off-label prescribing in a French hospital. *Pharm. World Sci.* 29, 97–100
- 27 Ufer, M. *et al.* (2003) Widespread off-label prescribing of topical but not systemic drugs for 350,000 paediatric outpatients in Stockholm. *Eur. J. Clin. Pharmacol.* 58, 779–783
- 28 Radley, D.C. *et al.* (2006) Off-label prescribing among office-based physicians. *Arch. Intern. Med.* 166, 1021–1026
- 29 Ekins, S. *et al.* (2011) *In silico* repositioning of approved drugs for rare and neglected diseases. *Drug Discov. Today* 16, 298–310