RESEARCH PAPER

Patent "Evergreening" of Medicine–Device Combination Products: A Global Perspective

« Perpétuité » des brevets pour les produits mixtes de médicaments et dispositifs médicaux : un aperçu mondial

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Abstract

Background: Patenting medicine-delivery devices (inhalers and pens) is controversial when it extends market protections beyond that of the underlying therapeutic agent. We evaluated how common device patenting is, internationally.

Method: Using a product sample (n = 88) and an international patent database, we assessed the issue's scope.

Results: When comparing the 88 patent portfolios for each product in each country, Canada was found to be among the most impacted, with 90% of the portfolios containing at least one device patent and 35% of the portfolios containing device patents exclusively.

Conclusion: Patenting of delivery devices impacts major pharmaceutical manufacturing centres worldwide. International consensus among stakeholders (regulators and payors) is needed on which device modifications represent meaningful clinical value.

Résumé

Contexte : Le brevetage des dispositifs d'administration de médicaments (inhalateurs et auto-injecteurs) suscite la controverse quand il étend la protection du marché au-delà de celle de l'agent thérapeutique sous-jacent. Nous avons évalué à quel point le brevetage des dispositifs est courant à l'échelle internationale.

Méthode : À l'aide d'un échantillon de produits (n = 88) et d'une base de données internationale sur les brevets, nous avons évalué la portée du problème.

Résultats : Après comparaison des 88 portefeuilles de brevets pour chaque produit dans chaque pays, le Canada figure parmi les plus touchés, avec 90 % des portefeuilles contenant au moins un brevet de dispositif médical et 35 % des portefeuilles contenant exclusivement des brevets de dispositif médical.

Conclusion : Le brevetage des dispositifs d'administration de médicaments a un impact sur les principaux centres de fabrication pharmaceutique dans le monde. Il est nécessaire de trouver un consensus international entre les parties prenantes (régulateurs et payeurs) au sujet des modifications de dispositifs qui représentent une réelle valeur clinique.

Introduction

Manufacturers of medicine–device combination products (e.g., inhalers, injector pens and patches containing one or more pharmaceuticals) often make successive modifications to the delivery device for a variety of reasons (e.g., to improve performance and for convenience) after the original regulatory approval. In doing so, patent protection on revisions of the device may be obtained, which would extend well beyond any patents protecting the active drug ingredient or its therapeutic formulation or the original device. The result is a medicine–device combination product with a longer period of market exclusivity, even when patents on the medication itself have long expired. This practice has become a point of controversy in Canada and several countries around the world (Blüher et al. 2019; Christie

et al. 2021; Daubner-Bendes et al. 2021; Ferrusi et al. 2009; Kaplan and Beall 2016; Moir 2021; Radelli 2021; Simoens 2008; Strohbehn et al. 2021), particularly when the patent protection garnered by the modified device confers more years of market protection than the patents protecting the medication itself.

For example, high prices on the EpiPen, which is used to deliver lifesaving (and patent-free) epinephrine during severe allergic reactions, caused major accessibility limitations in the US after recurring price hikes. Originally approved in 1987 with an older version of the delivery device, Mylan brought a new EpiPen into the market in 2011, which is protected by patents currently set to expire in 2025. This new set of patents pertained only to the injector pen (Duhigg 2017; Eunjung Cha 2016; Kasperkevic 2016; Rubin 2016). Among the new patented features of the injector pen were two locking assemblies "to hold the needle cover in a locked retracted and extended position" (US7449012) (Google Patents n.d.). While this assembly may be beneficial to patients in terms of safety, it also contributes to constrained access, especially given that epinephrine has been used safely for more than a century using other delivery devices.

Similar to the EpiPen, 14 other US Food and Drug Administration (FDA)-approved medicine–device combination products had patent protection for the delivery device alone, extending the period of market exclusivity for the medicine–device combination by a median of 9.0 years, including another epinephrine pen (AUVI-Q) with 14.2 years of device patent protection (Beall et al. 2016). The purpose of the current study is to extend previous country-specific investigations (Beall and Kesselheim 2018; Beall et al. 2016) of device patents to evaluate (a) the international scope of delivery-device patent filings, (b) how commonly combination products only have patent filings for the device in countries and regions worldwide and (c) to understand which countries or regions are potentially the most impacted by this issue based upon such patent filings.

Methodology

Overall design

Using the European Patent Office's (EPO's) International Patent Documentation (INPADOC) database (EPO 2022), we linked all the publication numbers associated with 88 combination products delivered via an inhaler, injector pen or patch that were identified through a previous survey of the FDA patent register (also known as the "Orange Book") to locate all related patent applications globally. For each country and region globally contained in the INPADOC, we then calculated the proportion of the combination products in our sample that had (1) at least one device patent application (among all the applications for that same product) and (2) only device patent applications (i.e., no applications were found for the substance or formulation).

Ethics

Institutional review board approval for this study was not required as no patients were involved. All data analyzed are publicly available online.

Data

We began with a previously published US dataset of medicine–device combination products (observation window from 2000 to 2016) with patents pertaining predominantly to the delivery device (i.e., the patent publication's title pertained to the device itself) (Beall and Kesselheim 2018). We included only inhalers, injector pens and patches (n = 88 of 144 products) as these represented the most common types of combination products. This dataset includes information about the products themselves (e.g., their FDA approval date), and links the patent to one of three categories: (1) a device patent (i.e., the patent title refers to the delivery device), (2) a substance patent (i.e., the patent covers the active ingredient or therapeutic compound) or (3) a formulation patent (i.e., the patent covers any other feature of the product not covered by the other two categories, such as its formulation, manufacturing process or indication). We augmented this dataset with the products' therapeutic classes using the first level of the World Health Organization's Anatomical Therapeutic Chemical Classification System (WHO 2021).

We further compiled an international patent landscape by entering all US patent numbers from our previously published dataset (Beall and Kesselheim 2018) into the EPO's INPADOC patent application database (EPO 2022); this linkage is necessary because there is no equivalent medicine patent register for Europe or elsewhere (Health Canada has a similar patent listing system, but device patents for combination products are not listable by law [Government of Canada 2021]). In doing so, we derived the INPADOC extended patent family for each FDA-listed patent (EPO 2017). INPADOC's patent families include all patent applications internationally related to the same initial (i.e., "priority") patent application: in other words, these include all applications internationally that can be traced back to the initial "parent" application made by the inventors in one jurisdiction in the world before they proceeded to file a trail of subsequent "child" filings elsewhere in the world (EPO 2022). The data extraction from INPADOC was performed in April 2020. Note that the international patent data extracted from INPADOC included both national and regional applications, and that not all patent applications translate to granted patents. For the present purposes, the term "jurisdiction" means both individual countries and regional patent regimes, wherein a single filing can be adopted by all countries within that consortium, including the African Regional Intellectual Property Organization (ARIPO), the Eurasian Patent Organization (EAPO), the EPO and the Organisation Africaine de la Propriété Intellectuelle (OAPI) (a patent regime for francophone African countries).

For national patent applications, we categorized countries according to their respective World Bank Classifications as high income, upper middle income, lower middle income or

low income (World Bank 2021). Using data from the article by Gapminder (2021), we also estimated the healthcare market size for all national jurisdictions by multiplying a country's per capita income by its population and by its percent national expenditure on healthcare (Beall et al. 2017).

Analysis

We first report descriptive statistics on our product sample dataset (n = 88), including the number of combination products, the type of product and the product's therapeutic areas. We then report on the number of patent applications found in INPADOC for the 88 products, as well as the range of jurisdictions in which they were located.

For each patent jurisdiction internationally, we calculated the proportion of the 88 combination products that had at least one patent application solely directed to the device. Then, we calculated the proportion of the same 88 combination products that only had device patent filings and no other patent filings of any other kind (i.e., no unexpired substance or formulation patents were located during our observation period). We plotted our results from these two analyses on a scatterplot to visualize how jurisdictions around the world compare in terms of (1) how commonly combination product patents in the US had at least one unexpired foreign device patent filing and (2) how commonly those combination products only had foreign device patent filings. When both indicators were high for a country or region, we reasoned that those areas would have an especially high stake in the debate surrounding delivery device innovation. All analysis programming was performed in R using TidyVerse (Tidyverse 2021); plots were generated using ggplot2 and ggrepel (Slowikowski 2021).

Results

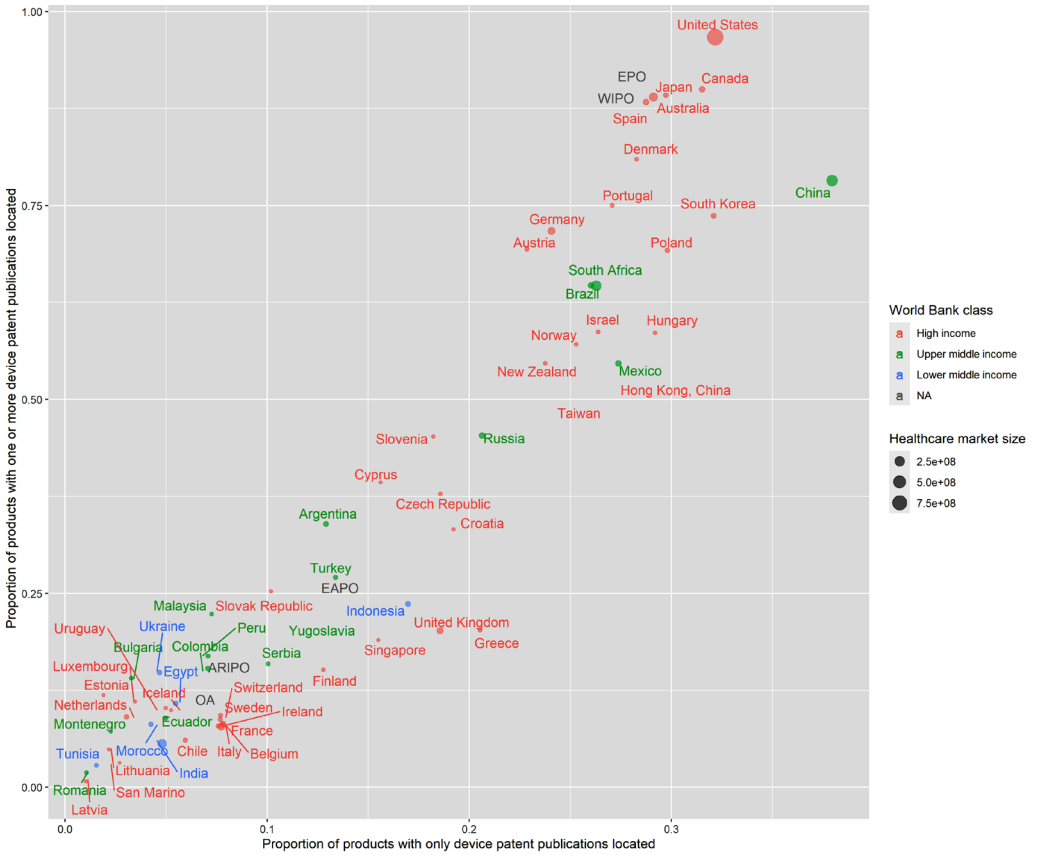
Of the 88 patented medicine–device combination products, 41 (47%) were inhalers, 31 (35%) were injector pens and 16 (18%) were patches. These products covered eight therapeutic areas, the largest of which were for respiratory disorders (37 devices, 42%), such as chronic obstructive pulmonary disease (COPD) and asthma; alimentary tract and metabolism disorders (24 devices, 27%), such as diabetes; and nervous system disorders (14 devices, 16%), including drugs for assisting with opioid dependence or tobacco cessation. We retrieved 7,622 international patent applications from INPADOC for the 431 FDA-listed patents relating to the 88 products. These patent publications were tied to 74 countries and five regional patent jurisdictions.

Proportion of combination products with at least one device patent filing

A number of countries and regions had similarly high proportions of products with device patent applications, particularly if they were in the higher income bracket (Figure 1: y-axis). For example, 90% (79/88) of the products had at least one device patent publication in Canada and the EPO (Table 1, available at longwoods.com/content/26973). This same

measure was 87% (78/88) in Australia, 87% in Japan (78/88) and 97% (85/88) in the US. Most of the original combination product sample also had at least one device patent publication in certain upper-middle-income countries (Figure 1: y-axis), including Brazil (65%, 57 products), China (78%, 69 products), South Korea (74%, 65 products) and South Africa (65%, 57 products) (Table 1). There were many other countries and regions where substantially fewer combination products had at least one patent publication specific to the device, such as ARIPO with just 14% (12/88) (Table 1; Figure 1: y-axis).

FIGURE 1. Proportion of product sample (n = 88) with at least one device patent filing versus device-only patent filings located in various locations around the world



The y-axis displays the proportion of the product sample (n = 88) in which at least one device patent filing was found in that country or region. The x-axis shows the proportion of the product sample (n = 88) for which only device patent filings were found in that country or region.
Countries are coloured by their World Bank income category and by the size of their healthcare sector, which was calculated by multiplying their per capita gross domestic product and their population size by their proportion of national spending on healthcare. As these same calculations were not possible for the regional patent regimes, only their names are displayed in the appropriate place in the plot.

Proportion of combination products with device-only patent filings

About one-third of the products (28/88) had device-only patent filings, depending on

TABLE 2. Number and proportion of products with device-only patent publications located in countries and regions around the world (n = 88)

Category	Count of jurisdictions in sample	Count of products with device-only patents detected
Income		
High	43	18%, n = 16 of 88 (IQR: 8–27%; n = 7–24)
Upper middle	22	11%, n = 10 of 88 (IQR: 7–22%; n = 6–19)
Lower middle	9	5%, n = 4 of 88 (IQR: 5–6%, n = 4–5)
Low	0	n = 0
Key countries		
Australia	1	30%, n = 26 of 88
Brazil	1	26%, n = 23 of 88
Canada	1	32%, n = 28 of 88
China	1	38%, n = 33 of 88
Japan	1	30%, n = 26 of 88
Korea	1	32%, n = 28 of 88
South Africa	1	26%, n = 23 of 88
United States	1	32%, n = 28 of 88
Regional patent filings		
ARIPO	1	8%, n = 7 of 88
EAPO	1	15%, n = 13 of 88
EPO	1	28%, n = 25 of 88
OAPI	1	7%, n = 6 of 88
WIPO (PCT)	1	28%, n = 25 of 88

Where device patents were located on one or more products within each jurisdiction, this analysis calculated the proportion of the number and of the product sample with only device patent filings. Products with only device patents are typically older products containing therapeutic substances and formulations whose patents expired before 2000 (i.e., the earliest patent register edition captured by this study).
ARIPO = African Regional Intellectual Property Organization; EAPO = Eurasian Patent Organization; EPO = European Patent Office; IQR = interquartile range; OAPI = Organisation Africaine de la Propriété Intellectuelle; WIPO (PCT) = World Intellectual Property Organization (Patent Cooperation Treaty).

the country or region (Table 2). For example, comparable proportions of products with device-only patent filings were observed for Australia (30%, n = 26 products), Brazil (26%, n = 23 products), Canada (35%, n = 28 products), China (38%, n = 33 products), the EPO (28%, n = 25 products), Japan (30%, n = 26 products), South Korea (32%, n = 28 products), South Africa (26%, n = 23 of 88) and the US (32%, n = 28 products). However, these proportions were somewhat higher than in other countries (Figure 1: x-axis) particularly in lower income settings, such as ARIPO (just 7 of the 88 products had device-only product patent publications).

Jurisdictions with device-only patent filings

Combination products with device-only patent filings were especially common in Australia, Brazil, Canada, China, the EPO, Japan, South Korea and South Africa (Figure 1: both x- and y-axes). Examples of products with device-only patent filings located in most, or all, of these top jurisdictions were typically for asthma, COPD, anaphylaxis and diabetes (Table 3, available at longwoods.com/content/26973).

Discussion

Canada is among those nations with the highest patent application filings pertaining to combination products' delivery devices worldwide, along with Australia, Brazil, China, Europe (EPO), Japan, South Korea, South Africa and the US. These areas of the world are critical centres for branded and generic pharmaceutical manufacturing for both domestic markets and export. Thus, concerns about manufacturers restricting access to older essential drug products using device patents is an international issue. Key stakeholders in these countries (e.g., public and private payors, drug regulators and health technology assessment authorities) should work collaboratively to build consensus on how to delineate the amount of innovation that would justify issuing patents on devices that deliver essential medicines, granting regulatory approval and providing reimbursement through public and private payors (Blüher et al. 2019; Daubner-Bendes et al. 2021).

The main reason why our searches only found patent applications pertaining to the delivery device for certain products is that those products are newer generations of older combination products. Any patents protecting the drug substances within these older combination products must have expired before 2000 and were thus not listed in the Orange Book to be identified by our study. Previous research has demonstrated that the life course of pharmaceutical products typically begins with the discovery and patenting of a new therapeutic substance, followed by the optimization and patenting of the substance formulation, followed by the optimization and patenting of any delivery devices (if relevant) (Beall and Kesselheim 2018; Beall et al. 2016). As a specific potentially patentable entity, delivery devices have many mechanical components, meaning it is possible to keep changing them, which could lead to many patent filings that can stretch over several decades (e.g., from an injector pen, to an injector pen with an analogue dose counter, to an injector pen with a digital dose counter, to an injector pen with a digital dose counter with audio, to an injector pen with a digital dose counter and Bluetooth connectivity to an app).

New versions of drug delivery devices can provide enhanced safety or convenience to patients. However, a superior clinical value should be demonstrated in clinical trials and not simply be assumed because changes to device technology can also disrupt patient care as healthcare providers must educate themselves and their patients on the use of the new version of the product. Discontinuation of older versions of devices can also interrupt patient adherence. Furthermore, some new versions of delivery devices have been recalled for faulty design, which also puts patients at risk for bad outcomes (Beall and Kesselheim 2018). In countries,

such as Canada, where healthcare delivery is a provincial responsibility, it is important to recognize the potential impact on patients and providers downstream. Key stakeholders, therefore, are not limited to actors at the federal level.

From an economic perspective, updating existing products' delivery devices increases product cost and the cost to society. The process of updating delivery devices may involve costly clinical trials before their approval, which must then be considered by regulatory authorities (an additional cost to society). Manufacturers must upgrade and retrofit equipment to produce the new delivery device, and quality assurance staff must be retrained. Should manufacturers withdraw original device designs from the market, the already, especially lengthy, regulatory process gets more complicated for generic drugmakers seeking to demonstrate equivalence with the now-discontinued products, for a variety of reasons (e.g., the regulatory body may be required to conduct an investigation to ensure that the product discontinuation was not made for safety reasons). Generic manufacturers seldom pursue drug-device markets, such as for inhalers, and in the absence of competition, drug prices can remain elevated (Conrad and Lutter 2019; Feldman et al. 2022). The additional patents, if challenged, must be defended in court by lawyers from both sides of the dispute. All activities such as these have cost implications that are passed onto and absorbed by patients and payors. Even a small increase in cost on a combination product can have a large impact at the health system level over time, deferring resources that could have been better spent elsewhere. This is particularly important for non-high-income settings such as those noted by our study (e.g., Brazil and South Africa). For example, an increase of just $0.25 per unit for the 36 million Americans living with an asthma or COPD diagnosis could cost upwards of $108 million per year, assuming an average of one new inhaler per month per patient. In countries such as Canada, where health technology assessment (HTA) plays an important role at the federal and provincial levels, HTA methodologies that evaluate the value of new versions of products with newly updated delivery devices against the value of older versions may play an important role in reimbursement decisions. Such evaluations are critical because new versions of combination products may not have superior clinical value for cost as compared with the original.

From an innovation policy perspective, other drug development activities might be overlooked in favour of the redevelopment of delivery devices. For example, developing new therapeutic substances occurs many years prior to regulatory approval. The substance is typically patented, then undergoes clinical trials, is considered for approval by regulatory authorities and is then approved. By the time that the product reaches the market, an average of 10 to 12 years of the 20 years of patent protection have already expired (Beall et al. 2019; Lexchin 2021). By contrast, modification of delivery devices for an existing product is more expedient, leading to fewer years of patent life lost during the pre-market phase. The upshot is that relatively more post-market patent protection is provided for delivery-device redevelopment as compared to the development of the therapeutic ingredients that they deliver. This sends a signal to developers to continue to devote increasingly more attention to

delivery-device upgrades, which may divert some resources away from other forms of pharmaceutical research and development that may have had a greater potential for a meaningful impact in those same clinical areas. Previous research has demonstrated that the number of device-only patents has come to far outnumber any other type of patent protection on these products in more recent years (Beall and Kesselheim 2018; Feldman et al. 2022). While alternatives or changes to the current patent system have been proposed elsewhere that would limit such activity (Beall et al. 2021; Feldman 2019; Vincent Rajkumar 2020), coordinating legal reform internationally would prove extremely challenging, particularly given the entrenchment of international trade agreements (e.g., the World Trade Organization's Trade-Related Aspects of Intellectual Property Agreement [WTO n.d.]). More expedient solutions may involve key stakeholders (e.g., major public and private payors) in the countries identified by our study refraining from reimbursing low-value products, including combination products that do not add clinical benefit beyond that of the original version of the device.

Our study has some important limitations. First, we did not account for regulatory exclusivities (e.g., drug regulatory bodies in some countries are barred from approving generic equivalents for a certain number of years) and other market protections (e.g., trade secrets) that may impact the combination product innovation landscape aside from patents. Second, we did not investigate predictors of where device-only patents have been filed, but the patterns observed in Figure 1 appear consistent with those noted by previous research on non-combination products, with market size and pharmaceutical manufacturing capacity being some of the most influential factors for where more patents tend to be filed (Attaran 2004; Beall et al. 2017). Third, because our methodological approach was to begin with the US market, to identify products with device patents and to extend the geographical reach by using INPADOC, our study is US- and Europe-centric. While INPADOC's patent data availability for other countries such as Australia and Canada is excellent, coverage of some key middle-income countries with high pharmaceutical manufacturing capacity, such as India, is limited. Fourth, as our US dataset had a patent register observation window extending from 2000 to 2016, many non-device patents for older products filed before 2000 would not be captured by our study. Therefore, our study has only captured the end stages of those products' innovation life courses, in which the only remaining innovation activities pertain to attempts to optimize the delivery device. Fifth, as our product sample was US-centric, many of the products in our sample may not be approved (or be relevant to general practice) in all countries as several have very specific indications in specialty care (e.g., a second-line therapy for polyarticular juvenile idiopathic arthritis). Lastly, while this study focuses on patent protection, we acknowledge the many other important challenges to generic market entry and motives for continuous delivery-device improvement, aside from intellectual property (Greene and Riggs 2015; Socal and Greene 2020). While patents may restrict a subsequent entrant from introducing an identical medicine–device combination product, this would not be the case for products for which both the device and the medicine have expired patents. For example, the originator EpiPen was introduced in the 1980s; current versions with active patents

are not the originator device, but newer versions of it. In this case, there is no patent barrier to introducing a generic delivery device, but there are other factors that discourage other market entrants, such as competition with an originator product that has benefitted from substantial marketing during its period of market exclusivity. Future research should seek to delineate patent rights from other barriers (financial, clinical evidence or others) and market forces that may disincentivize generic market entry.

Conclusion

Controversies over when pharmaceutical manufacturers have developed a new device to deliver an old drug with marginal health benefits to the patient is an international issue as the same patent families on such devices are located in important pharmaceutical markets and manufacturing centres worldwide, including Australia, Brazil, Canada, China, Europe, Japan, South Korea, South Africa and the US. While some countries are insulated from the same level of high prices on pharmaceutical products as the US (through price control policies), the same concerns still apply regarding unnecessary costs, disruption of patient care and the signal sent by the innovation system for manufacturers to continue to devote increasingly more innovation attention to delivery device upgrades. Stakeholders from within these key locations around the world should work together to build consensus on when patents for updated delivery devices should be supported through the granting of additional patents, approvals by regulatory authorities or reimbursement by public and private payors, including those at provincial or state levels.

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Competing Interests

Aaron S. Kesselheim has reported serving as an expert witness in a case against Gilead Sciences, Inc. related to patents of its Tenofovir-containing products.

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