INTERNATIONAL GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

Crowell

Gaming the system

An overview of originator companies' evergreening strategies used to hinder access to generic and biosimilar products

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Executive
Summary

This executive summary provides an overview of the key findings of the report "**Gaming the system – an overview of originator companies' evergreening strategies used to hinder access to generic and biosimilar products**". To contribute and enhance the necessary discussion to ensure a balanced system in which generic and biosimilar products are not improperly prevented from bringing competition to the market, this report assesses the myriad strategies used by some originator companies on both national and international levels to extend monopolies of their medicinal products beyond the intended terms. These strategies result in undue delays or the outright blocking of access to generic and biosimilar products, which adversely impacts access to affordable medicinal products for patients. The coexistence of the two fundamental healthcare objectives, "innovation" and "access", is constantly disrupted by evergreening practices. The report underlines the critical importance of maintaining high-quality patents, pro-competitive patent systems and robust legal and regulatory frameworks that facilitate timely competition from generic and biosimilar companies for the ultimate benefit of patients and healthcare systems.

This executive summary highlights a selection of the many strategies that lead to evergreening detailed in the report. For each strategy discussed here, the report offers additional concrete examples from various jurisdictions, to shed light on the complex dynamics of healthcare systems and the interplay between intellectual property, regulatory and market access rules that impact timely access to generic and biosimilar products.

Background

The pharmaceutical industry is a high-technology, knowledge-intensive and a highly regulated industry. Within this sector, while a net differentiation is hard to make, two main types of companies exist: originator companies, and generic and biosimilar companies.

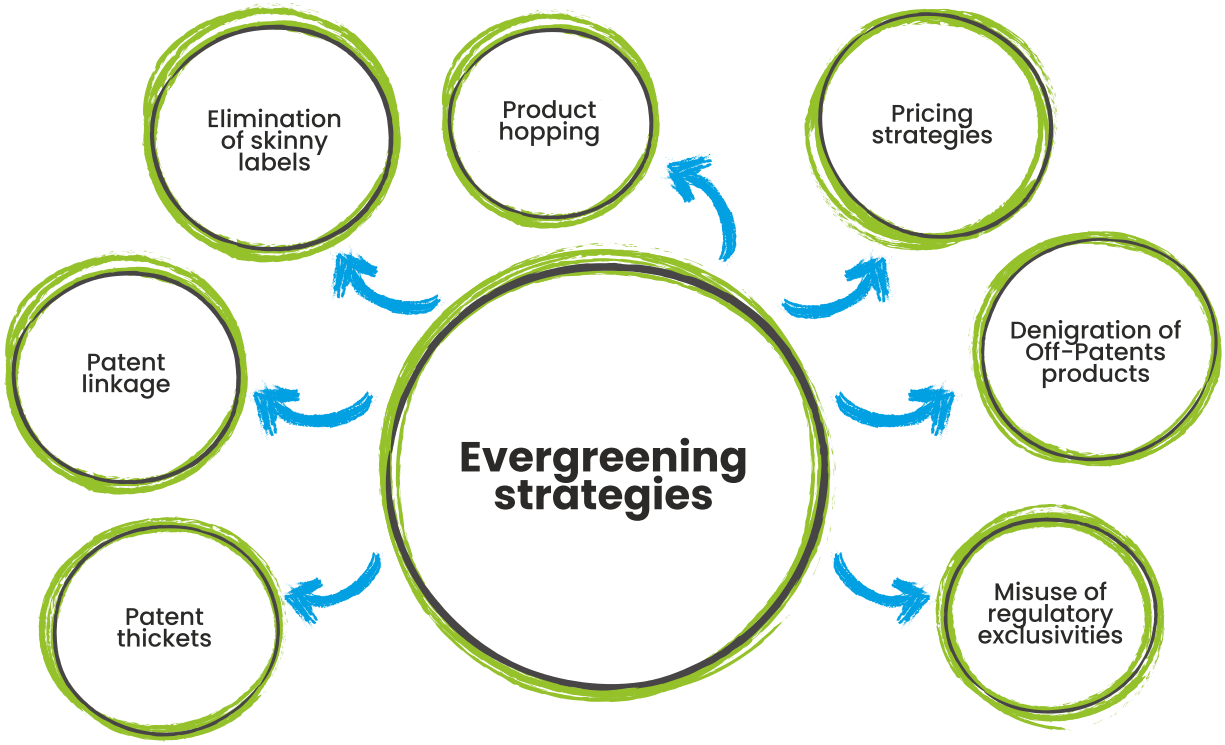
When the relevant market protections for originator companies' products expire, they face competition from generic and biosimilar products, which leads to lower prices of the medicinal products and often an increased number of doses in the market. Generic and biosimilar companies in all countries have proved their importance and contribution to access to medicinal products, both by volume of the pharmaceutical market they serve – more than

70% of the total volume of medicinal products dispensed globally[1] – and by effectively increasing access to treatment.[2] For this reason, generic and biosimilar companies play a very important role. They create competition, which not only drives innovation for new therapies but also reduces costs of medicinal products. By alleviating financial pressure on national healthcare systems, they significantly **improve patient access to affordable treatments**.

It is perhaps unsurprising, given the incentives to do so, that some originator companies employ various tactics to delay or block generic and biosimilar companies from entering the market at the earliest possible opportunity. This practice is often called "**evergreening**", and it is a systemic problem because it keeps affordable versions of medicinal products off the market, making healthcare more expensive, harder for patients to afford, and limiting the number of patients who have access to expensive medicinal products. As a result of evergreening strategies, patient access to cheaper treatment is delayed or even blocked, and, importantly, it reduces the stimulus to innovate for new therapies.

A myriad of evergreening strategies

Evergreening strategies take multiple forms and are used by originator companies worldwide, as illustrated below. The focus of this paper is **patent thickets, patent linkage, elimination of skinny labels, product hopping, pricing strategies, denigration and misuse of regulatory procedures**. They can have a material impact on the timing of generic launch, whether used individually or in combination. For some medicinal products, such as, for instance, MabThera® (rituximab) or Glivec® (imatinib), the originator company used the same evergreening strategies in parallel across multiple jurisdictions; for other medicinal products, such as Gilenya® (fingolimod) or Xalatan® (latanoprost), the originator company used multiple strategies in combination in the same jurisdiction.

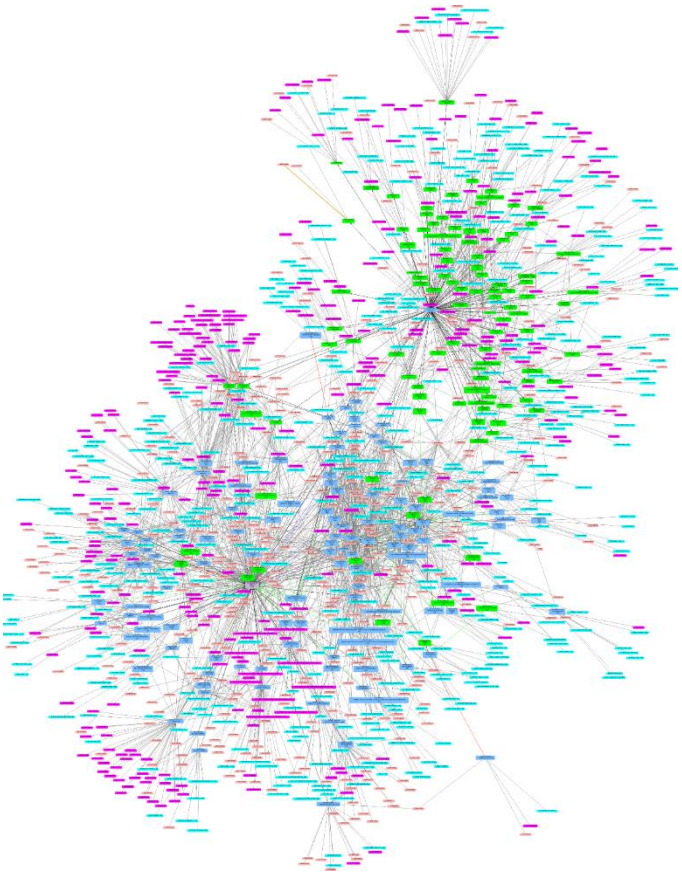


[1] See the market penetration by region: International Generic and Biosimilar Medicines Association, "Market Penetration of Generic Medicines" (2023) (See https://www.igbamedicines.org/doc/Market-Penetration-of-Generic-Medicines.pdf).

[2] In the past twenty years alone, the core seven therapy areas in 2000 that had the highest generic competition have continued to provide savings in the European Union while treatment volume has more than doubled, as described in IQVIA 2023 Biosimilar competition in Europe, page 7 https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2023.pdf.

01
Patent thickets

Originator companies intentionally misuse the patent system to extend the monopoly of the patented medicinal product by filing many patents on the same product. This includes filing patents on every aspect of a medicinal product as well as seeking multiple patents for the same invention. The result is the creation of a complex web of patents – often called patent thickets – designed to raise entry barriers for generic and biosimilar companies, hindering their ability to compete. By strategically obtaining and then enforcing these patents, originator companies can extend their monopoly for longer periods. Notably, patent thickets strategies are even more successful in jurisdictions where **preliminary injunctions** are allowed without any thorough assessment (or any assessment at all) of the actual validity or infringement of the patent. Just three of the many examples of patent thickets are Norvir® (ritonavir) and Keytruda® (pembrolizumab) in the United States and Trajenta® (linagliptin) in India.



Norvir® (ritonavir) – Global

The infographic below created by the World Intellectual Property Organisation (WIPO) shows the huge patent landscape of ritonavir in 2011, a medicinal product for the treatment of human immunodeficiency virus (HIV). From the first filing for this compound in July 1994, to the present filings in which additional patent families attempt to protect subsequent innovations to the compound, variants and derivatives, combinations with other chemicals, methods of production, methods of use, there are over 800 patent families directed to Ritonavir.

Source: WIPO, 'Patent Landscape Report on Ritonavir' (2011) - Patent Landscape Report on Ritonavir (wipo.int).[3]

[3] WIPO, 'Patent Landscape Report on Ritonavir' (2011). This WIPO report focuses on all the secondary patents that spun-off of the first ritonavir molecule patent, including "*liquid dosage formulations, solid dosage formulations, synthesis of Ritonavir and its key intermediates, and polymorphs and crystalline Ritonavir*". The report stresses that "*subsequent generations continue to narrow the scope of protection in a wide area of technologies while still maintaining protection from the first Ritonavir Patent, a phenomenon that is also sometimes termed "evergreening"*".

Keytruda® (pembrolizumab)

Keytruda® (pembrolizumab) is an expensive and important anticancer medicinal product, which costs around 165,000 USD per year of treatment. To extend its monopoly and continue making profits, as of October 2021, the originator company filed for 129 patents, with many more expected. If this patent thicket has the same effect on the timing of biosimilar products as a similar thicket created for Humira® (adalimumab), it could delay the launch of biosimilar products of pembrolizumab for several years after the expiration of these patents. The annual sales of Keytruda® increased by nearly 20% to approximately 25 billion USD in 2023 and are forecast to top 30 billion USD by 2026, so any delay to the launch of biosimilar products will have a massive impact on the healthcare system in the United States.

Trajenta® (linagliptin)

In relation to Trajenta® (linagliptin) and Trajenta Duo® (linagliptin; metformin), used to treat type 2 diabetes mellitus, the originator company initiated multiple patent infringement lawsuits in India in parallel before two courts in order to block the entry of several generic products. While one court issued preliminary injunctions preventing generic companies from launching until patent expiry, in the parallel case, one year later, the Delhi High Court reached a different outcome and rejected the preliminary injunctions request, stressing that "*by filing multiple patent claims in respect of the same invention, the plaintiffs have made an attempt towards evergreening the invention and re-monopolizing the same. […] The aforesaid conduct of the plaintiffs defeats the rights of the manufacturers of generic drugs such as the defendant companies and is also detrimental towards the public interest*." Additionally, the court ordered the originator company to compensate the generic companies financially.

As a result of this preliminary injunction strategy, generic companies were prevented from launching affordable and accessible products from February 22, 2022, until March 29, 2023.

02
Patent linkage

Another strategy that originator companies rely on to delay access to generic and biosimilar products is patent linkage. Patent linkage connects the approval, pricing, reimbursement or listing of a generic or biosimilar product to the status of patents of the originator company. Examples of this strategy, amongst others, are Esbriet® (pirfenidone) in Canada and Xalatan® (latanoprost) in the European Union.

Esbriet® (pirfenidone)

This tactic was applied by an originator company in Canada to delay a cheaper version of its medicinal product, Esbriet® (pirfenidone), from being sold. The originator company strategically sued the generic company to obtain a guaranteed delay to the approval of the generic product due to patent linkage. Even though the generic company eventually won the case, it took two years for the court to decide, during which time the less expensive version could not be sold, and the originator company was able to extend its period of monopoly.

Xalatan® (latanoprost)

The originator company in the European Union used this tactic for a medicinal product called Xalatan® (latanoprost), which is important for treating eye glaucoma. As a consequence, cheaper versions of the medicinal product were unduly kept off the Italian market for seven months, making it harder for patients to get affordable treatment. This delay cost the Italian healthcare system 14 million EUR. Eventually, the originator company was fined 13.4 million EUR for using this evergreening strategy to keep its monopoly longer in order to maximise its profits.

03
Elimination of skinny labels

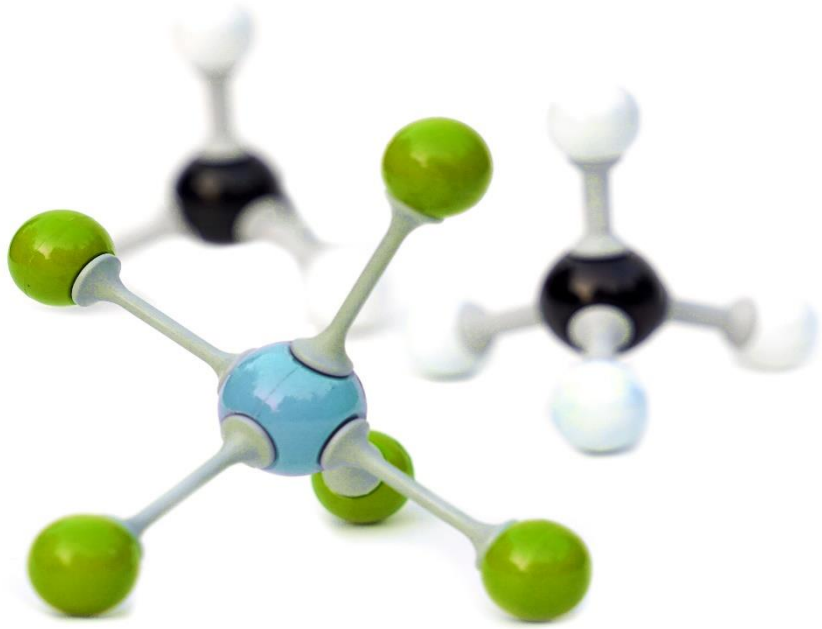
When there is a patent directed to an indication, a generic or biosimilar company may remove that patented indication from its label and launch its medicinal product for those indications for which patents have already expired – this is commonly called a "skinny label". This mechanism is crucial in ensuring that competition for the non-patented indications is not delayed. However, in practice, originator companies often seek to limit the scope of this mechanism, for example, amongst others, in Canada with Opsumit® (macitentan) and in the United States with Vascepa® (icosapent ethyl).

Opsumit® (macitentan)

In Canada, the originator company sued a generic company that intended to make an equivalent and cheaper version of Opsumit® (macitentan), which is used to treat pulmonary arterial hypertension. Even though the generic company fully removed the patented indication from its label, the court sided with the originator company. The court decided to limit how the skinny labelling mechanism could be used. This has delayed access to the off-patent indications significantly.

Vascepa® (icosapent ethyl)

The originator company filed suit for infringement of patents against a generic company in the United States, notwithstanding the disclaimers and the skinny label. The originator company argued that the generic company specifically intended to actively encourage physicians to directly infringe the asserted patents by prescribing its generic version of Vascepa® (icosapent ethyl). As a result of the court's decision, generic and biosimilar companies face legal uncertainty and must be extremely cautious in making statements about their medicinal products when they are opting for a skinny label approach to avoid claims of infringement.



04
Product hopping

Originator companies often introduce slightly modified or next-generation versions of their medicinal products just before the expected competition on the original version. They then encourage the market to switch to the new version, which is typically protected by newer, later expiring patents. Often, they discontinue the original product entirely, effectively forcing patients to the new version. For example, originator companies might replace a capsule with a tablet that has a longer patent, allowing them to extend their monopoly and profits. This tactic is called product hopping. When timed properly, that medicinal product switch can render generic and biosimilar products developed for the original version obsolete, resulting in millions of dollars of wasted development cost, and delay to competition for medicinal products containing that active ingredient. Even without patents on the newer medicinal product, this product can still materially impact the launch of generic and biosimilar products. This strategy is clearly demonstrated by, amongst others, Namenda IR® (memantine) in India and Gaviscon Advance Liquid® (sodium alginate and potassium hydrogen carbonate) in the United Kingdom.

Namenda IR® (memantine)

This tactic has been applied in India by an originator company that makes a medicinal product called Namenda IR® (memantine) in tablet form, which is used to treat Alzheimer's disease. The originator company decided to discontinue the medicinal product and replace it with a new version called Namenda XR® (memantine) in capsule form. As a result, doctors started prescribing the more expensive new version capsules instead of the tablets with significant impact on competition, the healthcare budget and patient access to generic products.

Gaviscon Advance Liquid® (sodium alginate and potassium hydrogen carbonate)

In anticipation of the launch of generic products, the originator company launched in the United Kingdom a new version called Gaviscon Advance Liquid of an old medicinal product called Gaviscon Original Liquid. Both medicinal products have the same active ingredient. The originator company withdrew the original medicinal product, Gaviscon Original Liquid, from the NHS database, widely used by prescribing doctors. Because of this, doctors were led to prescribe Gaviscon Advance Liquid. The UK competition authority found evidence that the company did this on purpose to prevent generic companies from successfully selling generic versions of the earlier medicinal product. The originator company ultimately admitted infringing UK and European competition law and agreed to pay a penalty of 10.2 million GBP.

05
Pricing strategies

Originator companies apply various pricing strategies, such as, for instance, predatory pricing, whereby they deliberately set the prices of medicinal products at unreasonably low levels to force generic and biosimilar companies to exit the market or deter their entry or expansion. This practice can be clearly identified, amongst others, in Argentina in the context of MabThera® (rituximab) and in the European Union in the context of Herceptin® (trastuzumab).

MabThera® (rituximab)

This tactic was adopted in Argentina with a cancer medicinal product called MabThera® (rituximab). The originator company tried to keep biosimilar rituximab products off the market by setting the price of its rituximab below its product costs in the most critical public tender, but eventually, these versions entered the market and saved around 4.4 million USD each year. Without this strategy, the growth of the biosimilar in the market would have been higher. If all patients switched to the cheaper versions, the savings for the Argentinian healthcare system could reach 7.8 million USD. The same company applied a pricing tactic for the same medicinal product also in Uruguay. As a result, the company had been fined 814,496 USD by the Uruguayan antitrust authorities, considering its practice as a case of tying sales. The fine was then revoked by the Uruguayan courts, which did not consider it an illegal conduct.

Herceptin® (trastuzumab)

In the European Union, the originator company commercialising a cancer medicinal product called Herceptin® (trastuzumab) was fined 9,47 million EUR by the Romanian competition authority and the anti-competitive behaviour was confirmed by the High Court of Cassation and Justice. The originator company was fined for distorting competition from biosimilar companies forcing the exclusion of biosimilar products from a tender, which meant that patients could not get more affordable treatment. This behaviour led to lost healthcare savings of approximately 7.1 million EUR for the Romanian healthcare budget.

06
Denigration of generic and biosimilar products

Originator companies may introduce a strategy to mislead doctors about generic and biosimilar products to make patients and prescribers fear that they are not as safe and effective as the reference medicinal product. This tactic is called the denigration of generic and biosimilar products. They do this to influence public opinion and encourage patients to continue buying the more expensive (yet equivalent) original medicinal products. This practice is identified, amongst others, in the European Union for Durogesic® (fentanyl).

Durogesic® (fentanyl)

In December 2017, the French Competition Authority found that an originator company had abused its dominant position and consequently delayed the arrival of the generic version of Durogesic® by: (i) trying to convince the French agency for medical safety of health products not to grant at national level the generic status to competing medicinal products, despite this status already having been obtained at European level; and (ii) implementing a massive campaign of falsely disparaging the generic version and using misleading language to create doubt in the minds of healthcare professionals about the effectiveness and safety of these generic products.

This combined strategy was effective, having influenced over half of French pharmacies, which led to a very low penetration levels of the generic product.

07
Misuse of regulatory exclusivities

Originator companies may not only misuse the protections granted by patents, but they may also misuse regulatory exclusivities, such as data exclusivity and market exclusivity periods. When these regulatory exclusivities expire, generic and biosimilar companies are allowed to enter the market, increasing patient access to affordable treatment. However, originator companies often attempt to prolong the regulatory exclusivities as long as possible to keep their monopoly and continue generating substantial profits. The misuse of regulatory exclusivities is identified, amongst others, in the European Union for Glivec® (imatinib) and in Mexico with Humira® (adalimumab).

Glivec® (imatinib)

In the European Union, the originator company successfully extended the regulatory exclusivities of its multi-billion cancer medicinal product called Glivec® (imatinib - with annual sales of 4.65 billion USD globally in 2015) by obtaining orphan exclusivity of a similar product in its portfolio, Tasigna® (nilotinib – with annual sales in 2015 of 1.63billion USD). Because of this, it took six additional years for affordable versions of Glivec® to become available, i.e. in 2017 instead of 2011. This meant that patients had to wait six years longer for more affordable treatment.

Humira® (adalimumab)

In Mexico, the system of regulatory exclusivities can be misused by originator companies, since data exclusivity can be prolonged by 5 years every time a new indication on a medicinal product is approved. In this way, the holder of the marketing authorisation for Humira® managed to extend the data exclusivity protection that was attached to the original adalimumab (i.e. five years from the granting of the original marketing authorisation in 2003) from May 2008 to at least 2024, thus delaying biosimilar competition by sixteen years.

The importance of patent quality

At the heart of most of the strategies above is a granted patent, so ensuring that only the highest quality patents are granted in the first place is essential. As described above, once a patent is erroneously granted, it can lead to costly litigation and delayed entry of cheaper generic and biosimilar products. This, in turn, negatively affects access to affordable treatment and significantly increases healthcare costs for society.

It is evident that as a monopoly right, a patent is **an exception to the fundamental principle of free competition**. This exception is established in legal systems to incentivise innovation. However, such a monopoly should be granted only when it is necessary to encourage innovation, namely where the invention is genuinely novel and inventive, and that the scope of the patent accurately reflects the innovation achieved and disclosed. The Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) provides for such minimum requirements which are then adopted by member countries of the World Trade Organisation (WTO).

It is important to recognise that once a patent is granted, the cost associated with challenging and invalidating it often exceeds both the cost of developing a generic product and the fees required to maintain the patent. Litigating the question of whether a patent is valid and infringed across major markets worldwide can cost well in excess of 10 million USD.

All agencies interested in the sustainability of healthcare systems must therefore ensure that patent offices are properly resourced, not rewarded for granting poor quality patents, constantly trained and updated on the science in the relevant field by independent experts and fully empowered to require full and honest answers from patentees. They should also ensure that there is a robust, well-resourced and consistent way to challenge patents at the local patent office, such as pre- and post-grant oppositions.

A balanced intellectual property system is essential for fostering innovation while ensuring access to affordable medicinal products. To achieve this balance, patentees, patent offices, regulatory bodies and competition authorities must all accept their roles in ensuring that patents are only granted when they are truly deserved and that the pharmaceutical systems stimulate timely access to competition.

Disclaimer:

This report compiles an illustrative number of cases investigated and/or decided by courts/authorities, as well as cases where certain evergreening practices have been implemented but limited due to safeguards within national systems. The report does not provide an exhaustive list of evergreening strategies, cases and examples, and opinions reflected herein, if any, are solely based on the evergreening practices available in the public domain. The collection of cases and the resultant opinions presented in this report have been shared by IGBA members, illustrating strategies employed by originator companies in markets where IGBA members are present, based on the data sourced from public domain. As such, therefore, the report and/or opinions are also limited in terms of its geographical scope and cases/investigations, as well as of the status or final outcome of the court/administrative proceedings that are referred to.

Glossary

Active ingredient	The main ingredient in a medicinal product that causes the desired effect of the product. Some medicinal products contain more than one active ingredient acting in different ways in the body.
Biosimilar product	A biological medicinal product that is highly similar to the reference product. Biosimilar products are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicinal products.
Data exclusivity	A regulatory protection of reference products that starts with the marketing authorisation of the reference product. During this period, generic and biosimilar companies cannot refer to the data of the reference product for the approval of their generic or biosimilar product.
Denigration of generic and biosimilar products	Originator companies communicate negative messages to the market about the safety and efficacy of generic and biosimilar products in an effort to persuade the public or healthcare professionals that they are inferior, thereby improperly preventing the prescription of generic and biosimilar products.
Divisional patent application/divisional	A type of patent application that contains subject-matter from a previously filed application. It is intended to be used where the parent application lacks unity of invention.
Evergreening	Strategies of originator companies aimed at extending their exclusivity by delaying or blocking market entry of generic and biosimilar companies and by taking advantage of the different layers of protections they enjoy in order to extend the profitability of their reference products for as long as possible.
Generic and biosimilar companies	Companies that develop and manufacture versions of reference products developed by the originator companies and can market them after expiry of relevant patent and regulatory protections. They create or increase competition and reduce the costs of medicinal products.

Generic product	A medicinal product that is developed to be the same as the reference product. A generic product contains the same active ingredients as the reference product, and it is used at the same dose(s) to treat the same disease(s). Generic products are manufactured according to the same quality standards as all other medicinal products.
Market exclusivity	A regulatory protection of reference products that starts with the marketing authorisation of the reference product. During this period, generic and biosimilar products cannot be placed on the market.
Marketing authorisation	The approval by a regulator to market a medicinal product in a given jurisdiction.
Originator company	Companies that invest in research and development of new medicinal products and/or that bring new medicinal products to the market.
Parent patent	The first patent application submitted for a new invention and to which a divisional patent refers.
Patent	The official legal right to make or sell an invention in a given jurisdiction for a particular number of years. For medicinal products, the length of all patents is twenty years.
Patent linkage	A practice linking the regulatory approvals status of a generic or biosimilar product to the status of a patent or patents for the reference product.
Patent term extension	An extension of the protection provided by a patent and granted to compensate the time it takes for a newly patented product to obtain a marketing authorisation. It has different names in different regions, such as patent term restoration, supplementary protection certificate, etc.
Patent thicket	A complex tapestry of overlapping intellectual property rights that poses a significant challenge for generic and biosimilar companies seeking to bring cost-saving generic and biosimilar products to the market.

Predatory pricing	The setting of prices at an unreasonably low level (below a cost parameter) by an originator company to induce a generic or biosimilar company to exit the market or to deter its entry or expansion.
Preliminary injunctions	An interlocutory order issued by a judge early in a legal proceeding to stop the defendant from continuing their allegedly harmful behaviour.
Product hopping	A strategy used by originator companies to delay competition by launching slightly modified versions of their medicinal products shortly before generic or biosimilar companies are expected to enter the market, and either discontinuing the reference product or reducing the price of the new product to force prescribers to move to the new product.
Reference products	New medicinal products brought to the market by originator companies. These medicinal products are generally protected by multiple patents and regulatory protections for a certain period of time. The reference product is the existing medicinal product already on the market to which generic and biosimilar products are developed to be similar.
Regulatory exclusivities	Exclusive rights, including data exclusivity and market exclusivity, granted to companies that bring new medicinal products to the market, allowing them to sell these products for a specified period of time in exchange for making the invention public, and providing a reward and incentive for innovation.
Secondary patents	Used to refer to all patents filed on a reference medicinal product other than those that claim the active ingredient itself. These will be filed at a later phase in the development of the medicinal product, and cover other aspects of the medicinal product such as different dosage forms, formulations, production methods, etc.
Sham litigations	A practice in which an originator company files baseless court claims solely to harass and deter generic or biosimilar companies from entering the market, rather than having a legitimate grievance, with the aim of eliminating competition.

Skinny labelling	A regulatory approach allowing generic and biosimilar products to be approved for non-patented indications, enabling timely market entry by carving out patented indications from their labels.

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Introduction

Introduction

Background

The pharmaceutical industry is a high-technology and knowledge-intensive industry and is highly regulated and complex. In general terms, the sector has two different types of enterprises:

- "Originator companies" are the companies that bring new medicinal products to the market. These companies sometimes conduct the research and development of those new products in-house but also very regularly acquire those products from smaller companies or academic institutions. It is typically the role of these large originator companies to perform the clinical trials essential to ensuring that new medicinal products are safe and effective before they are brought to market. Once that new medicinal product is approved by a regulatory authority, it becomes a "reference product" for generic and biosimilar companies.

  Reference products are generally protected by multiple patents and regulatory protections (data exclusivity and market exclusivity) for a certain period of time. Patent protection and regulatory protections provide originator companies with a market monopoly, allowing to recoup investments and generate profits before competition from generic and biosimilar companies entering the market.

- "Generic or biosimilar companies" develop and produce versions of the originator companies' medicinal products for sale after the expiry of the relevant protections and upon obtention of the due marketing authorisation from the corresponding regulatory authority. Generic and biosimilar products must meet the same rigorous regulatory standards for quality, efficacy and safety as reference products.

  Generic and biosimilar companies play a crucial role in the healthcare systems, creating competition, reducing costs of medicinal products and pressure on healthcare budgets, thereby improving patient access to affordable medicinal products.

When the relevant patent and regulatory protections have expired, originator companies face competition from generic and biosimilar companies. This competition from more affordable generic or biosimilar products impacts revenue streams of the originator companies. In response to this challenge, originator companies often engage in various legal and market tactics to extend their monopoly by delaying or blocking market entry of generic and biosimilar companies. They take advantage of the various layers of protections in combination with sophisticated market strategies, exploiting the inherent complexities of the different legal systems. These tactics aimed at "evergreening" the protections are intended to extend the reference products' profitability for as long as possible. However, the impact of evergreening is significant: it results in the delay or outright blocking of more affordable generic or biosimilar versions of the reference products, thereby increasing healthcare costs for society, to the detriment of the patient: access to affordable medicinal products is reduced.

The global market entry of generic and biosimilar companies results in savings for healthcare systems worldwide and increases patient access to medicinal products significantly. For example, medicinal products from Indian

companies alone provided 219 billion USD in savings to the healthcare system in the United States (U.S.) in 2022 and a total of 1.3 trillion USD between 2013 and 2022.[4]

The European Commission calculated that generic market entry reduces prices of medicinal products by as much as 80% to 90% in the European Union.[5] As a result, in 2014, generic products led to estimated savings of 100 million EUR[6] and biosimilar list price savings accounted for 5.7 billion EUR in 2020 alone.[7] Since 2000, the expenditure on the largest therapy areas (i.e. cardiovascular, antibacterial, and cholesterol) has decreased from 37% of the total pharmaceutical expenditure to 8% thanks to the availability of generic treatments.[8] In addition, the European Commission concluded that, between 2000 and 2007 alone, if generic companies had entered the market without undue delays, European healthcare budgets would have saved at least 20% more (around 3 billion EUR) than they actually did (15 billion EUR) due to the delay of market entry.[9] In relation to biosimilar products in the European Union, between 2016 – 2021, the cumulative savings at list prices deriving from biosimilar products doubled every two years, with the total cumulative savings now reaching 50 billion EUR.[10]

But the huge contribution of generic and biosimilar products is not limited to savings; it also leads to a significant increase in access to medicinal products, with selected jurisdictions indicating generic market penetration ranging from 70 to 97%.[11] In fact, in the past twenty years alone, the core seven therapy areas in 2000 that had the highest generic competition have continued to provide savings in the European Union while treatment volume has more than doubled.[12] For example, since 2005, generic products have reduced the price of anti-ulcer treatment by 83%, while supporting a 145% increase in volume.[13] This means that several patients only have access to better treatment when generic or biosimilar products enter the market. Hence, the fundamental importance of timely access to the market for generic and biosimilar products.

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[4] IQVIA Institute, "U.S.-India Medicine Partnership – India's contribution to the U.S. healthcare system" (2024) (see https://www.ipa-india.org/wp-content/uploads/2024/05/IQVIA-US-India-Medicine-Partnership.pdf).

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[8] Beneath the Surface: Unravelling the True Value of Generic Medicines iqvia.com/-/media/iqvia/pdfs/library/white-papers/iqvia-true-value-of-generic-medicines-04-24-forweb.pdf.

[9] European Commission (Competition DG), 'Pharmaceutical Sector Inquiry – Final Report' (see https://competition-policy.ec.europa.eu/system/files/2022-05/pharmaceutical_sector_inquiry_staff_working_paper_part1.pdf), para. 64 to 94); Csiszár P. 'Delay in generic entry should remain a concern to competition authorities. Journal of Generic Medicines'. 2012;9(3):123-127. doi:10.1177/1741134312456695).

[10] IQVIA 2023 Biosimilar competition in Europe, page 5 https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2023.pdf.

[11] International Generic and Biosimilar Medicines Association, "Market Penetration of Generic Medicines" (2023) (See https://www.igbamedicines.org/doc/Market-Penetration-of-Generic-Medicines.pdf).

[12] IQVIA 2023 Biosimilar competition in Europe, page 8 https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2023.pdf.

[13] IQVIA 2023 Biosimilar competition in Europe, page 8 https://www.iqvia.com/-/media/iqvia/pdfs/library/white-papers/the-impact-of-biosimilar-competition-in-europe-2023.pdf.

As a result, any barrier that delays or prevents the market entry of generic and biosimilar companies has a significant impact on the cost and accessibility of healthcare. Even though evergreening strategies are being used throughout jurisdictions, there is no universally accepted definition of this concept.[14] For the purposes of this paper, it refers to any strategy or practice employed by originator companies that improperly delays or constrains the launch of generic or biosimilar products at the earliest opportunity foreseen by the law.

The concept of evergreening extends beyond patents, and this report clearly demonstrates that originator companies deploy a variety of strategies that go beyond patent-related tactics. These sophisticated strategies take place in parallel in various jurisdictions encompassing regulatory and non-patent issues, the interplay with regulatory procedures and enforcement. This report aims to highlight the multifaceted efforts by some originator companies to extend their monopoly by leveraging a combination of legal, regulatory and market strategic manoeuvres.

Evergreening is therefore also used to label practices that extend the monopoly of an originator company by seeking trivial improvements or adjustments to a medicinal product and switching the market to that new medicinal product. Such medicinal products are the result of marginal innovation on existing products, in such a way that confers no major therapeutic improvement. Such strategies are often also called "lifecycle management", a practice of moving the market to medicinal products with minor variations of the reference product – new forms of release, new dosages, new combinations or variations, or new forms, changing a medicinal product from a tablet to a capsule etcetera – and sometimes obtaining patents for those minor changes. This has the effect of delaying competition for that active ingredient, while not delivering any significant innovation or therapeutic benefit for patients.[15]

With respect to evergreening strategies using patents, the World Health Organization Commission on Intellectual Property Rights, Innovation and Public Health defines evergreening as a term popularly used to describe patenting strategies "*when, in the absence of any apparent additional therapeutic benefits, patent holders use various strategies to extend the length of their exclusivity beyond the 20-year patent term*".[16] Evergreening in the context of patents is possible across numerous jurisdictions worldwide due to the relatively low threshold for obtaining patents, which often leads to the issuance of low-quality patents.[17]

The report outlines various market and legal strategies that contribute to the practice of evergreening. The objective of this report is to promote balanced pharmaceutical legal and regulatory systems that foster innovation and allow for the timely launch of generic and biosimilar medicinal products. It aims to support fair competition and mitigate the risks of evergreening globally, emphasising a patient-centric approach as fundamental.

This analysis is not meant to suggest that patents inherently obstruct competition. On the contrary, the International Generic and Biosimilar Medicines Association (IGBA)

[14] R. F. Beall, J. W. Nickerson, W. A. Kaplan, A. Attaran, "Is Patent "Evergreening" Restricting Access to Medicine/ Device Combination Products?" (2016) PLoS One 8.
[15] L. P. Lukose, "Patent ever greening: Law and Ethics" (2016) ICIL, 1; WIPO, "The Changing Face of Innovation" (2011) WIPO Economics & Statistics Series, 186.
[16] World Trade Organization, World Intellectual Property Organization and World Health Organization, "Promoting Access to Medical Technologies and Innovation – Intersections between public health intellectual property and trade" (2020) 172.
[17] Ibid.

believes that patents serve as one of the vital incentives for fostering innovation, provided that these patents are of high quality.

Methodology

The methodology of this report is based on an assessment of cases investigated and/or decided by courts/authorities, as well as instances where certain evergreening practices have been implemented but were limited due to safeguards within national systems. The report does not provide an exhaustive list of evergreening strategy cases and examples. Instead, it presents a collection of cases shared by IGBA members, illustrating strategies employed by originator companies in markets where IGBA members are present. As such, therefore, the report is limited in terms of its geographical scope and cases/investigations.

Structure of the report

The structure of this report is organised to provide a comprehensive overview of evergreening strategies. The report is divided into the following Sections:

1 focuses on patent-related strategies:

1.1 investigates the impact on generic and biosimilar companies as a consequence of the misuse of divisional (or continuation) patents, resulting in patent thickets as a result of the filing of multiple, overlapping patents.

1.2 explores the impact of the misuse of the patent linkage systems on the timely availability of generic and biosimilar products.

1.3 looks at how second medical use patents and skinny labelling mechanisms are used to hinder or delay generic and biosimilar products.

1.4 assesses how preliminary injunctions are successfully used as an evergreening strategy, and

1.5 describes the practice of sham litigations used to increase the cost and complexity of litigation for generic and biosimilar companies, and delay cost-saving competition.

2 focuses on the importance of patent quality for medicinal products.

3 relates to non-patent strategies (although patents can also play a role in these approaches):

3.1 identifies the practice of product hopping, in which slight modifications to a medicinal product are made to shift the market to a new, often patented, version.

3.2 discusses pricing strategies, focusing on predatory pricing, where the prices of reference products are set at a below-cost level to undermine competition, and

3.3 investigates the impact of the denigration of generic and biosimilar products to influence public opinion, and hinder the uptake of generic and biosimilar products.

4 relates to the interplay with regulatory procedures:

4.1 evaluates how generic and biosimilar companies' market entry is delayed focusing on the challenges associated with obtaining reference products, and,

4.2 describes how regulatory protections are misused, including data exclusivity and market exclusivity.

5 provides a conclusion and a possible way forward.

Patent issues

Patent thickets

1. Patent issues

1.1 Patent thickets

It is both possible and common for an originator company to obtain many patents covering a reference product, as well as a vast range of claims that do not cover the reference product but other non-commercialised versions of that product. They amass these patents in two ways:

- by filing patents over every possible aspect of the medicinal product – the active ingredient, the various forms and salts of the active ingredient, formulations, manufacturing processes, methods of use or indications, dosage regimes, impurities – the list goes on, and
- by filing multiple copies of each of these patent types. This second approach leads to the creation of what is called a patent family – that is multiple patents that all have the same application but may have slightly different claims, and in which the first patent filed is called the "parent" of that family.

The most common way of obtaining these multiple copies is by filing a divisional patent application, often referred to as a "divisional" and/or a continuation in the U.S. Divisional applications were created to address the situation where the parent application lacks unity of invention, i.e. includes more than one invention and, therefore, the applicant splits the parent into one or more divisional applications each claiming only a single invention. The subject matter of a divisional application cannot extend beyond the scope of the earlier application, nor the protection period. When used in this manner, it is a legitimate way to split an initial parent application that contains multiple inventions. However, in most countries, there are no restrictions on when a patentee can seek a new divisional patent or on how and when a divisional application can be withdrawn and then re-filed again. As a consequence, in the life sciences space, most divisionals are typically not filed in response to a unity objection from a patent examiner, but filed voluntarily by the patentee. This tool, therefore, allows patentees to obtain a thicket of patents, to expand the scope of the inventions covered by that patent family and/or to delay final resolution of the validity of that patent family.

This divisional abuse has the most impact in the period after the primary patent covering the medicinal product *per se* has expired, and is applied to the secondary patents that may protect specific attributes of the product, such as, for example, specific indications, patient groups or formulations. In the pharmaceutical sector, originator companies often intentionally misuse divisional patents as an evergreening strategy to extend the enforceable life of patents as much as possible.

Obtaining certainty regarding a patent family can be difficult if it has multiple divisional patents/applications. And it can get even worse if these divisional applications are withdrawn right before a decision on them is taken and a new, almost identical, divisional application is filed. This is for three reasons:

- it allows a patentee to avoid a final decision on the validity of that patent family for an extended period of time;
- it allows a patentee to obtain a huge number of patents for the same invention all of which need to be separately challenged at significant cost and risk; and

- it allows the patentee to expand and tailor the scope of the claims of those later family members in order to capture other medicinal products that were outside the scope of the parent.

As noted, a patentee can avoid or delay a final decision on validity through divisionals. If there is a concern that one patent in the family – let's say the parent patent – will be challenged, an originator company will have at least one

pending divisional application in that family. Before a final decision on that parent patent is issued, the originator company can effectively withdraw that parent patent, forcing generic or biosimilar companies seeking certainty regarding the validity and scope of that patent family to re-start the challenge on the next member of the patent family, wasting generic and biosimilar company resources, patent office resources and potentially delaying launch while those subsequent rounds of patent challenges are resolved.

Finally, originator companies use their divisionals to obtain patents that are not directed to their own medicinal product, but that are specifically drafted to capture generic and biosimilar products. While there is one specific medicinal product that has been the focus of the research and development spend of an originator company, the claims of a patent thicket can be shaped over time to capture other products that fell outside the scope of the parent patent. This means that a generic and biosimilar company can never effectively design around members of a patent family as they change over time to capture medicinal products that were not previously covered by that patent family.

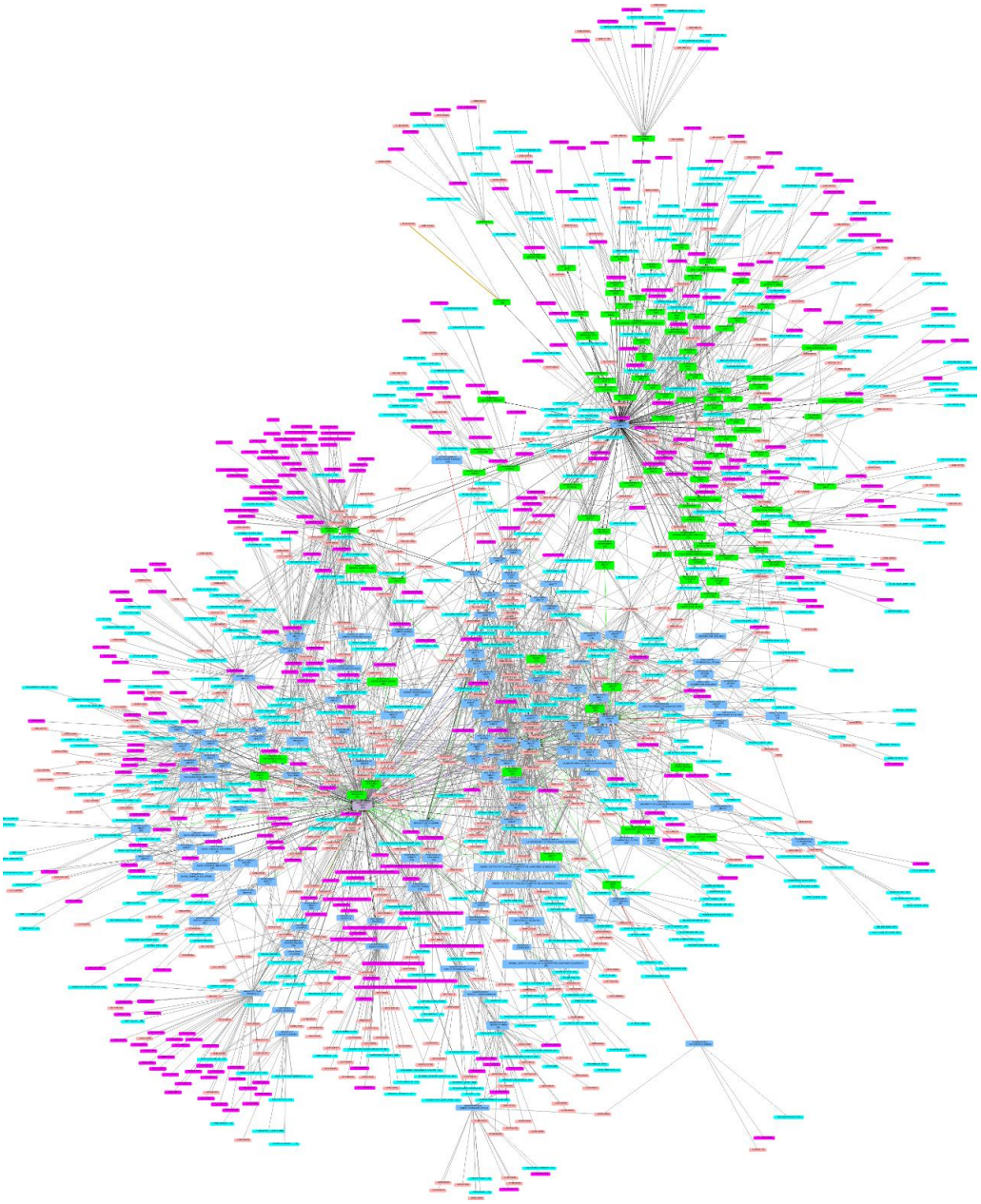
Originator companies can, therefore, also obtain what can be described as "divisional patent thickets" – that is large numbers of patents to that same invention. Indeed, originator companies are known to file multiple "follow-on" or "secondary" patent applications to further extend a medicinal product's patent protection (i.e. the patent on the molecule). This is done in the hope that at least one of the numerous "follow-on" patent applications will be granted and survive a litigation challenge. This results in an extensive "thicket" of patents being formed around a medicinal product, which may act as a barrier to entry for generic and biosimilar products. Attempting to resolve patent uncertainty when faced with multiple patents is an extremely expensive and time-consuming process for generic and biosimilar companies, even if all of the "follow-on" patents are weak (and not able to stand up to judicial scrutiny). Therefore, such patent thickets are used to create uncertainty and to prevent generic and biosimilar companies from launching their medicinal products.

The use of divisional patents and patent thickets takes place worldwide. The examples described for each jurisdiction relate not only to divisional patent thickets but also to thickets of secondary patents more broadly.

A significant example of patent thicket relates to Norvir® (ritonavir):

Norvir® (ritonavir)

The infographic below created by the World Intellectual Property Organisation (WIPO) shows the huge patent landscape of ritonavir in 2011, a medicinal product for the treatment of human immunodeficiency virus (HIV). From the first filing for this compound in July 1994, to the present filings in which additional patent families attempt to protect subsequent innovations to the compound, variants and derivatives, combinations with other chemicals, methods of production, methods of use, there are over 800 patent families directed to Ritonavir.



Source: WIPO, 'Patent Landscape Report on Ritonavir' (2011) - Patent Landscape Report on Ritonavir (wipo.int). [18]

[18] WIPO, 'Patent Landscape Report on Ritonavir' (2011).

This WIPO report focuses on all the secondary patents that spun-off of the first ritonavir molecule patent, including "*liquid dosage formulations, solid dosage formulations, synthesis of Ritonavir and its key intermediates, and polymorphs and crystalline Ritonavir*". The report stresses that "*subsequent generations continue to narrow the scope of protection in a wide area of technologies while still maintaining protection from the first Ritonavir Patent, a phenomenon that is also sometimes termed "evergreening"*".

1.1.1. Argentina

In Argentina, divisional patent applications are often used improperly to create uncertainty among generic and biosimilar companies and to delay Argentina Patent Office rejection decisions. This strategy aims to keep patent applications – and therefore their enforceability – alive that would otherwise have already received a final rejection from the Argentina Patent Office.

A real-world example of the impact on the budgets of consumers and funders of this strategy can be found by looking at Glivec® (imatinib).

Glivec® (imatinib)

The originator company could not obtain a compound patent for imatinib as Argentina did not allow patents for medicinal products before October 30, 2000. Therefore, imatinib was always in the public domain in Argentina. However, the originator company deployed an intensive evergreening strategy including, but not limited to, divisional patent applications for secondary patents.

Firstly, the originator company filed eight patent applications related to different polymorphic forms and compositions of imatinib. Secondly, the originator company initiated patent infringement lawsuits with requests for preliminary injunctions against two generic companies. None of the lawsuits were won by the originator company.[19] Thirdly, in 2005, the originator company initiated four "strategic lawsuits" to declare the approval regime for similar medicinal products unconstitutional and revoke the marketing authorisations for imatinib obtained by generic companies. The lawsuits were rejected in all cases with decisions from the three chambers of the Federal Civil and Commercial Court and the Supreme Court of Justice of Argentina.

However, despite all these lawsuits ultimately being dismissed, the multiple judicial actions initiated by the originator company had a significant impact on the market by unduly delaying generic companies. In the case of Richmond, the preliminary injunctions resulted in four years of obstacles and uncertainty regarding the possibility of commercialising its generic product. For one generic company, the preliminary injunction delayed the launch of the generic company by two years. Other generic companies directly decided not to launch a generic product due to the originator company's actions. The negative impact on the budgets of consumers and funders could be estimated at least 42.6 million USD during the 2006 – 2011 period.

[19] Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala III, 3/7/2012, "Novartis AG c/ Laboratorios LKM S.A. s/ cese de uso de patentes" (n° 11.565/07); Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala I, 16/6/2011, "Novartis AG c/ Laboratorios Richmond SACIYF s/ medidas cautelares" (n° 5080/2007).

The Argentina Patent Office has implemented the *"Guidelines for Pharmaceutical and Biotechnological Inventions"* since 2012.[20] These guidelines aim to tackle the issues of evergreening and patent thickets by giving instructions for the evaluation of secondary patents, including polymorphs, pseudo-polymorphs (hydrates and solvates), enantiomers, selection patent applications, salts, esters, and other derivatives of known substances, prodrugs, metabolites, formulations and compositions, combinations, dosage/dose, second uses, and analogous processes. The Guidelines do not automatically deny secondary patent applications. Instead, they provide general instructions, and any exceptions must be duly justified.[21] Thus, a claim for a subject matter may be granted a patent if the applicant can prove its novelty, inventive step, industrial application, and so on. The Guidelines have been proven to be an effective policy for preventing evergreening, including patent thickets, making it easier to launch generic and biosimilar products in Argentina. Data shows that genuine pharmaceutical innovations are regularly granted patents, while evergreening patents are generally denied. According to Sampat and Shadlen[22], the introduction of the Guidelines resulted in a decrease in the grant rate for secondary patent applications from 9% to less than 1%.

1.1.2. Brazil

In Brazil, divisional patents are included in Law No. 9,279/1996, in Articles 26 to 28, which state that a patent application may be divided into two or more, *ex officio* or at the request of the applicant, until the end of the examination, provided that the divisional patent makes specific reference to the original application and does not exceed the disclosed matter contained in the original application. As in other jurisdictions, the divisional patents will have the filing date of the original application and the benefit of priority of the latter, if applicable, and each divisional patent will be subject to payment of the corresponding fees.

In January 2023, the Brazil Patent Office, the National Institute of Industrial Property, created Order 15.50 for "Notification of filing of a divisional patent" to facilitate the identification of divisional patents and their relationship with the original applications. The order allows the user who follows the publications of a given application to be notified of any divisional patent filed in Brazil. Before the existence of this order, it was difficult to identify all parent patents and their divisional patents.

In some cases, divisional patents are used as a strategy to increase the scope of protection of the parent patents or to seek to mitigate the risk caused by a parent patent application that is in the process of being rejected. Pertinent (non-exhaustive) examples of molecules with divisional patents in Brazil that contribute to legal uncertainty can be found in the table below.

[20] Joint Resolution No. 118/2012, 546/2012 and 107/2012, Adoption of Guidelines for the Examination of Patent Applications of Chemical and Pharmaceutical Inventions, Ministerio de Salud [Ministry of Health], Ministerio de Industria [Ministry of Industry], and Instituto Nacional de la Propiedad Industrial [Industrial Property National Institute], B.O., May 8, 2012.
[21] Ibid.
[22] Sampat, Bhaven N. and Shadlen, Kenneth C. (2017) "Secondary pharmaceutical patenting: A global perspective". Research Policy, Elsevier, vol. 46(3), pp. 693-707.

Brand name / INN	Parent patent	Divisional patent
Eylea® (aflibercept)[23]	BR112021025158	BR122023012219
	BR112021025359	BR122023012764
Imbruvica® (ibrutinib)	BR112014030424	BR122023011068
	BR112017018931	BR122023020985
Eliquis® (apixaban)	BR112012021337	BR122021013077
	BR112012021337	BR122021025189

1.1.3. Canada

Canada's divisional application system is one of the most restrictive ones. In relation to Canadian patents, divisional applications are permitted by Section 36 of the Patent Act only where an application is deemed to describe more than one invention. Divisional applications in Canada maintain the filing date and priority date(s) of the patent. A divisional patent may be filed at any time prior to the grant of the parent application, either at the initiation of the applicant or as directed by the Commissioner of Patents. The term of a divisional application is twenty years from the filing date of the parent application.

While pending divisional applications can potentially be exploited to create risks for potential third-party market entrants, there has not been significant jurisprudence in Canada regarding this practice. However, third parties are only able to challenge any divisionals by an attack on the validity of the issued patent(s) pursuant to Subsection 60(1) of the Patent Act. These challenges can be difficult, as the primary doctrine that can be raised in respect of divisional applications is that of improper double-patenting which is often met with a response from the patentee that there is no mischief caused by the presence of multiple patents on account of each patent having the same end to their term by virtue of Subsection 36(4) of the Patent Act.

A pertinent example of the use of patent thickets in Canada can be found regarding Humira® (adalimumab) and Cialis® (tadalafil), resulting in significant litigation costs for the generic and biosimilar companies involved.

[23] And also: BR122023012890 (divisional from BR112021025432); BR122023012149 (divisional from BR112021025438); BR122023012686 (divisional from BR112021025769); BR122023012848 (divisional from BR112022001016).

Humira® (adalimumab)

Multiple biosimilar companies were ultimately licensed to enter the Canadian market in early 2021[24], nearly four years after the compound patent expired. Prior to that time, JAMP Pharma Corporation ("JAMP") challenged three of the originator company's Humira® patents (CA 2,504,868; CA 2,801,917; and CA No 2,904,458). JAMP challenged these patents on grounds including obviousness, lack of patentable subject matter, anticipation, and overbreadth.

The court invalidated two patents (868 and 917) for obviousness but declared one patent (458) valid. However, the court did not grant the originator company a permanent injunction against JAMP, despite JAMP conceding to infringement of the 458-patent, citing public interest in avoiding forced switching to less ideal biosimilar products.[25] Eventually, after significant efforts and resources to challenge those patents, JAMP launched in April 2022.

Cialis® (tadalafil)

The originator company began selling Cialis® 10 and 20 mg tablets for treating erectile dysfunction in Canada on November 28, 2003. The originator company listed five patents on the Health Canada Patent Register, which is a feature of Canada's patent linkage system, and asserted all five listed patents against more than sixteen generic companies from 2012 to 2017.

Three of the generic companies spent more than a combined 13 million USD to defend against the originator company's infringement actions, but recovered less than 3.5 million USD in cost awards:

Generic company	Legal fees (USD)	Disbursements (USD)	Total (USD)	Recovered (USD)	Unrecovered (USD)
Apotex[26]	7,599,757	789,647	8,389,404	2,169,045	6,220,359
Mylan[27]	3,119,433	141,888	3,261,321	878,218	2,383,103
Teva[28]	1,159,941	194,052	1,353,993	371,260	982,733

[24] https://gabionline.net/biosimilars/news/Latest-launches-for-adalimumab-biosimilars-in-Canada-and-Japan.
[25] Federal Court of Canada, AbbVie Corporation and Abbvie Biotechnology Ltd v JAMP Pharma Corporation, 2023 FC 1520.
[26] 2023 FC 3.
[27] 2023 FC 13.
[28] 2023 FC 9.

1.1.4. European Union

In relation to European patents, divisional patents are provided for by Article 76 of the European Patent Convention, which specifies that the subject matter of any divisional patent application cannot extend beyond the scope of the earlier application as filed nor beyond its protection period. As with other countries, the intention of this provision was to allow a patentee to separate out multiple inventions from the one patent application. However, in practice, these are used to extend the examination period by the patent office, as the examination of divisional applications continues even if the parent application is withdrawn or revoked, which creates legal uncertainty for developers of generic or biosimilar products. For the patentee, the advantage of divisional applications is that they are deemed to have the same date of filing (and enjoy any right to priority) as the parent application. As a result, anything published between that filing/priority date and the date the applicant applies for a divisional cannot be relied upon to invalidate that patent. Therefore, a European patent application may give rise to multiple divisional patent applications, which, themselves, may give rise to multiple divisional patent applications, leading to multiple generations of divisional patent applications.

In this way, the divisional patent system may be exploited to create legal uncertainty for third parties, as the scope of the claims may change throughout the prosecution of a patent presenting an undefined blocking position over a prolonged period.[29] The uncertainty manifests in the increased risk of patent infringement issues on launch of the generic or biosimilar product, which can crystallize in either:

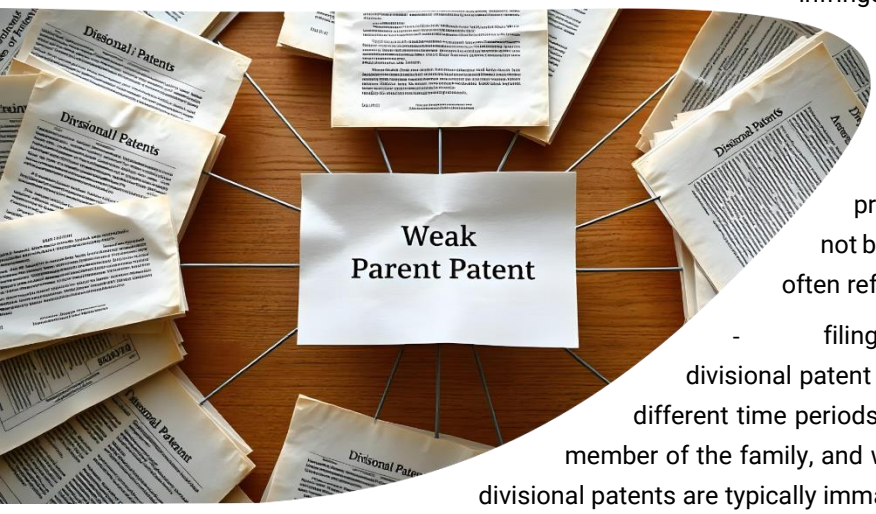
- a litigation risk, which can lead to proceedings being commenced in any and all national courts, which can be costly to defend against.
- having the launch blocked by the granting of a preliminary injunction. Or
- creating a risk for potential damages to be awarded by a national court, even if the divisional patent is later revoked in national proceedings or at the European Patent Office, whether at the Opposition Division or at the Technical Board of Appeal.

Moreover, divisional patent applications may be filed at the European Patent Office at any time while the earlier parent patent application is pending, even after generic or biosimilar companies have lodged applications for marketing authorisation for their generic or biosimilar products, or even launched the medicinal product into the

[29] Misuses of divisional patent applications were identified as problematic in the European Generic Medicines Association (EGA – now Medicines for Europe) Report, "Patent-related Barriers to Market Entry for Generic Medicines in the European Union", May 2008, available at: https://www.medicinesforeurope.com/wp-content/uploads/2009/06/EGA-IP_Barriers_web.pdf.

market. In this way, the divisional patents could encompass the generic or biosimilar product within their claims. The uncertainty this creates can present a significant barrier to generic and biosimilar companies seeking to legitimately bring their medicinal products to market.

It is only possible for an opposition before the European Patent Office or a revocation action before a national court to be brought once the patent has been granted, thus those companies looking to market generic or biosimilar products are forced to wait a significant period of time to obtain any certainty as to whether their medicinal product infringes a patent.



This sophisticated use of strategies around divisional patents in the European Union frustrates the judicial and administrative procedures inherent in the patent system, thus prolonging the enforceable life of patents that may not be able to stand up to judicial scrutiny. This practice, often referred to as the "divisional game" can involve:

- filing "cascades" of divisional patents, where each divisional patent related to the same weak parent patent is filed at different time periods, most often just before the grant of the previous member of the family, and where the differences between the claims of such divisional patents are typically immaterial.
- defending opposition proceedings (often such opposition proceedings can take between three and six years until final resolution by the Technical Board of Appeal of the European Patent Office).
- enforcing such patents in national courts, even via preliminary injunctions against generic or biosimilar companies.
- using the divisional patent to block pricing and reimbursement procedures for generic and biosimilar products (i.e. a patent linkage that in the European Union is considered unlawful).
- strategically withdrawing an opposed patent from the family, just before the Opposition Division or Technical Board of Appeal of the European Patent Office issues a decision regarding the validity of that patent, thereby frustrating the judicial process by shielding the patent family from judicial scrutiny for a prolonged period. Any new opposition proceedings in respect of later filed divisional patents would then take another three to six years until final resolution by the European Patent Office.

The legal uncertainty created by this strategy is even higher, with an increased risk of patent infringement, in scenarios where a patent thicket has been generated and divisional patent applications are filed from numerous secondary patents, subsequently used to block or delay regulatory or administrative approvals of generic and biosimilar products (i.e. patent linkage - see Section 1.2).

While there may be valid and objective reasons to withdrawing a divisional patent, the filing of an opposition limits what a patentee can voluntarily do with respect to that opposed patent. Under Article 105a of the European Patent Convention, a patentee can voluntarily limit or revoke its own patent. However, it is not permitted to do so while opposition proceedings in respect of the European patent are pending. This is a clear policy directive that patentees should not be permitted to avoid the effect of an opposition by voluntarily revoking or limiting their patent.

Some national jurisdictions have adopted local rules designed to prevent a patentee from filing "cascades" of divisional patents as referred to above.[30] Also the European Patent Office attempted to limit abuses of divisional applications by imposing a deadline for the filing of any divisional patent applications in reaction to the findings of the European Commission's Pharmaceutical Sector Inquiry Report published in 2009 that divisional patents were being abused.[31] However, this led to an initial influx of divisional patent applications that stretched the European Patent Office's limited resources and, after a consultation and some effective lobbying from patentees, the deadline was removed on 1 April 2014.

Some national courts (e.g. the UK and the Netherlands) have also tried to provide certainty to generic and biosimilar companies in the form of what have become known as "Arrow declarations".[32] In effect, this is a declaration from the court that a specific generic or biosimilar product or process was known or obvious at the priority date of that patent. The effect of such a declaration is that the specific generic or biosimilar product could not infringe any patent in that family, making that product immune to future divisionals. However, this practice has been of limited practical use, since the patent holder may simply withdraw the national designations of the relevant patents and divisional patent applications, and undertake not to designate future divisional patent applications in the relevant country. Whilst this can provide certainty for that jurisdiction, it does not overcome the uncertainty that generic and biosimilar companies face in other European jurisdictions.[33]

Some countries, such as Germany and Italy, apply a local concept of "unfair competition" to prevent the illegitimate use of a patent when such strategies lead to an unfair competitive advantage. However, this is only available in limited jurisdictions and national courts have only used this concept in isolated cases.[34]

The misuse of the patent system has been determined by the European Commission in the context of Spiriva® (tiotropium bromide). There are additional relevant pending matters, including in relation to divisional patents, that are being reviewed by the European Commission and may, in the future, provide in the future more clarity and guidelines, including for example a matter relating to Copaxone® (glatiramer acetate).

[30] See the Whitepaper "Anatomy of a failure to launch: a review of barriers to generic and biosimilar market entry and the use of competition law as a remedy", November 2020. Available at: https://www.medicinesforeurope.com/docs/2020.11.04-Medicines-for-Europe-Whitepaper.pdf.

[31] See the Pharmaceutical Sector Inquiry Final Report, European Commission, 8 July 2009, available at: https://competition-policy.ec.europa.eu/system/files/2022-05/pharmaceutical_sector_inquiry_staff_working_paper_part1.pdf.

[32] See the case Arrow Generics v Merck, District Court The Hague, related to alendronate in which the District Court of the Hague granted the declaration sought, finding that the generic alendronate tablets were an obvious modification of the state of the art. In 2019, the District Court of the Hague confirmed its jurisdiction to grant Arrow Declarations in Pfizer PFE B.V. v. F. Hoffmann-La Roche AG, Roche Nederland B.V., District Court The Hague, 8 May 2019, NL:RBDHA:2019:4515.

[33] A good overview on the divisional patent strategies and Arrow Declarations is provided in the article: "The devil is in the divisional: an analysis of divisional patents, deadlines, declarations and suggestions for future practice", by Mieke Filler, published by the Oxford University Press, Journal of Intellectual Property Law & Practice, 2024, Vol. 00, No. 00.

[34] See the decision of the Munich District Court "Verbot des Fallenlassens von Patenten" of 24 February 2020 (docket no. O 1456/20) and the decision of the Consiglio di Stato in relation to latanprost of 12 February 2014 (693/214).

Spiriva® (tiotropium bromide)

The European Commission investigated allegations by Almirall against the originator company. Almirall accused the originator company of filing unmeritorious patents related to treatments for chronic obstructive pulmonary disease, which could potentially block or delay the market entry of Almirall's generic products.[35]

The European Commission suggested the originator company and Almirall find a mutually acceptable solution to their dispute within the limits of European antitrust rules. Following this suggestion, the parties reached a settlement agreement that addressed the European Commission's concerns. As part of the settlement, the originator company agreed to remove the alleged blocking positions for the European Union, grant a license for two countries outside the European Union, and end the ongoing litigation between the parties. This agreement allowed Almirall to proceed with launching its combination medicinal products after obtaining marketing authorisation from the competent bodies. The European Commission concluded that the settlement between the parties was the most efficient and speedy way to ensure that consumers would benefit from Almirall's generic product and closed the case.

The settlement and the European Commission's intervention highlighted the importance of competition law in the pharmaceutical sector and its role in preventing misuse of the patent system that could hinder competition and delay the introduction of generic products.

In addition, there are many other examples clearly identifying the misuse of the divisional patent system by originator companies as an evergreening strategy, starting with historical examples and moving to products where we can see the patent portfolios necessary to engage in evergreening already developing.[36] A selection of examples can be found in Drovelis® (estetrol and drospirenone); Esbriet® (pirfenidone); Palexia® (tapentadol); Entresto® (valsartan and sacubitril); Xalatan® (latanoprost); and Gilenya® (fingolimod).

Xalatan® (latanoprost) – Divisional game and patent linkage

Xalatan® is a critical medicinal product for eye glaucoma. The original patent (EP 1 225 168) was set to expire in September 2009. The originator company filed for, and obtained, a divisional patent (EP 0 364 417) followed by a supplementary protection certificate and a paediatric extension.

In Italy, the combination of the originator company's divisional patent, supplementary protection certificate and unlawful patent linkage strategies successfully managed to extend the duration of its monopoly by seven months until May 2010. The Italian competition authority found evidence that the sole purpose of this strategy was to delay the onset of generic competition in the Italian market. The Italian Council of State confirmed this decision on appeal in 2014. A fine of 13.4 million EUR for the originator company was confirmed by the Italian

[35] See https://ec.europa.eu/commission/presscorner/api/files/document/print/en/ip_11_842/IP_11_842_EN.pdf.
[36] Additional cases are also documented in the Whitepaper "Anatomy of a failure to launch: a review of barriers to generic and biosimilar market entry and the use of competition law as a remedy", November 2020. Available at: https://www.medicinesforeurope.com/docs/2020.11.04-Medicines-for-Europe-Whitepaper.pdf.

Supreme Court in January 2024.[37] In addition to delaying patient access to generic treatment, this evergreening strategy cost the Italian Health service 14 million EUR in lost savings.[38]

Drovelis® (estetrol and drospirenone) – Patent thickets (future) and skinny label

The originator company has obtained many patents that will prevent generic companies from including key safety information in its summary of product characteristics, making it difficult to carve out patented information: (i) the combination of estetrol with drospirenone was patented with a supplementary protection certificate to 2027; (ii) the combination medicinal product is protected by regulatory exclusivities up to May 2029 (data exclusivity) and May 2031 (market exclusivity); and (iii) there are also multiple different applications related to the safety of the medicinal product.[39]

In addition, there is another patent family in the European Union that is limited to orodispersable tablets.[40]

Esbriet® (pirfenidone) – Divisional game and skinny label

A lot of the patents applied for by the originator companies referred to issues related to the safety of the medicinal product, as explained in the summary of product characteristics, therefore, making it very difficult for generic companies to consider a "skinny label" strategy, since the inclusion of safety related information in the generic summary of product characteristics is required.

The key exclusivities protecting pirfenidone were an orphan marketing exclusivity until March 2, 2021, and a compound patent and associated supplementary protection certificate that expired on September 17, 2021. However, the originator company applied for many other patents covering the various uses of pirfenidone, formulations, safety aspects and dosing regimens,[41] eleven of which were opposed by over nine different companies, with the first opposition filed in 2012. All but one of those patents were ultimately revoked.

However, for four of those patents, the originator company voluntarily abandoned the opposed patent, rather than allowing the European Patent Office to issue a written decision on the validity of the patent. For all four of those patents, there was another patent still in force in the same family, i.e. there was a patent in force with the same claims as the revoked patent. The choice by the originator company to withdraw those patents meant that generic companies were denied the certainty of a written decision on the validity of these patent families, forcing them to launch at risk of ultimately paying patent infringement damages.

[37] Decision no. 9/2024 published on 2 January 2024.

[38] See https://www.medicinesforeurope.com/wp-content/uploads/2023/10/Updated-Medicines-for-Europe-Bolar-Patent-Linkage-Paper-20-Oct-2023-1.pdf.

[39] EP 3749327 A1 if granted; expiry date 07 February 2039: Related to a contraceptive method having a reduced risk of venous thromboembolism (VTE) (associated with drospirenone), comprising administering to a female subject an amount of estetrol and drospirenone; EP 4135709 if granted; expiry date 16 April 2041: Combined oral contraceptive of estetrol (10-20 mg) and drospirenone (1-5 mg) providing a reduced risk for side effects, including a reduced risk for QT interval prolongation, a reduced risk for decreased testosterone and a reduced risk for elevated C-reactive protein levels, when compared to other combined oral contraceptives; WO2023/152682 if granted; expiry 09 February 2043: Contraception with reduced likelihood of scheduled bleeding in a woman having a BMI > 30.0 kg/m^2 and contraception with an increased likelihood of scheduled bleeding in a woman having a BMI < 30.0 kg/m^2 with administration of 24 days E4+DRSP and 4 days hormone free.

[40] EP 3310333 (expiring in June 2036) and EP 3701944 (expiring in June 2036).

[41] A selection of examples includes, amongst many others, EP 1965797 B1 (expiring in November 2026), claiming the prevention of dizziness, a side effect associated with the use of pirfenidone when administered at dosage of 2400 2403 mg/day; EP 2191831 (expiring in November 2029), related to modifying pirfenidone treatment for patients with atypical liver function. A series of divisionals were filed later on, all of them pertaining to the same patent family as EP 831; EP 2308491 (expiring in March 2030), covers the use of pirfenidone by patients who smoke. This patent was granted without opposition; EP 2324831 (expiring in March 2030) related to avoiding, contraindicating or discontinuing concomitant use of pirfenidone and fluvoxamine was revoked after opposition.

In practice, this systemic misuse of the patent system wasted significant resources at the patent office and generic companies (estimated opposition costs for the 29 filed oppositions of around 3.5 million EUR) and created a significant disincentive for generic companies to launch this product before 2030.

Entresto® (valsartan and sacubitril)

The strategy displayed here shows the interest of the originator company to always have a divisional patent live so as to create uncertainty and block generic companies while the parent patent and subsequent divisionals are facing opposition. This can be very clearly seen from the family related to the crystalline complex based on the parent patent EP 1948158 (expiring in November 2026, with a supplementary protection certificate up to November 2030). Although the parent patent survived the oppositions filed by third parties and was maintained as granted, the originator company voluntarily decided to withdraw it in May 2023. But while doing so, it kept on prosecuting the divisional EP 2340828 with a very similar scope. This patent is facing opposition/appeal proceedings and the oral proceedings are estimated in March – April 2026. In addition, another divisional EP 3685833 is still pending.

Gilenya® (fingolimod) – Divisional game and patent linkage

The originator company has been using the divisional patent system in conjunction with unlawful patent linkage in several EU Member States.[42] The strategy employed by the originator company appears to have been designed to extend the period of patent prosecution before the European Patent Office, with the aim of maintaining the divisional application pending as long as feasible, and of obtaining a granted patent as close as possible to the expiry of the market exclusivity for Gilenya®. It has employed the following steps as part of an overarching strategy: (i) the filing of a number of patent families containing multiple divisional patent applications, with each application having a later filing date, to create cascades of divisional patent applications; (ii) the strategic withdrawal of earlier patent applications in the cascades that have an almost identical subject matter to later patent applications in the cascades; and (iii) the aggressive enforcement of the latest of the patent applications (dosage patent (EP894)) before the courts, even before this patent application was granted in October 2022, seven month after the expected generic entry date on March 23, 2022. This strategy started from an initial patent application filed in 2006, i.e., sixteen years earlier.

In addition, across the EU Member States, the originator company has knowingly and deliberately intervened in the pricing, reimbursement and market access mechanisms for generic fingolimod products. In some cases, it appears to have done so in an underhand manner. This coordinated campaign of intervention appears to be an attempt to engineer "unlawful" patent linkage across the European Union, independent of any enforcement before the courts, and thus prevent and/or delay generic entry of fingolimod products. A very detailed description of the strategy used in this case is described in a 2022 Medicines for Europe Letter to the European Commission.[43] This evergreening strategy led to a delay of generic products in two ways: (i) generic companies had to defend against preliminary injunctions in the different jurisdictions across Europe, and were preliminarily enjoined from launching in Denmark, Italy, Sweden, Spain, Belgium, Czechia, Poland and Greece; and (ii) those generic companies that have refrained from launching have therefore suffered a delay of almost two and a half

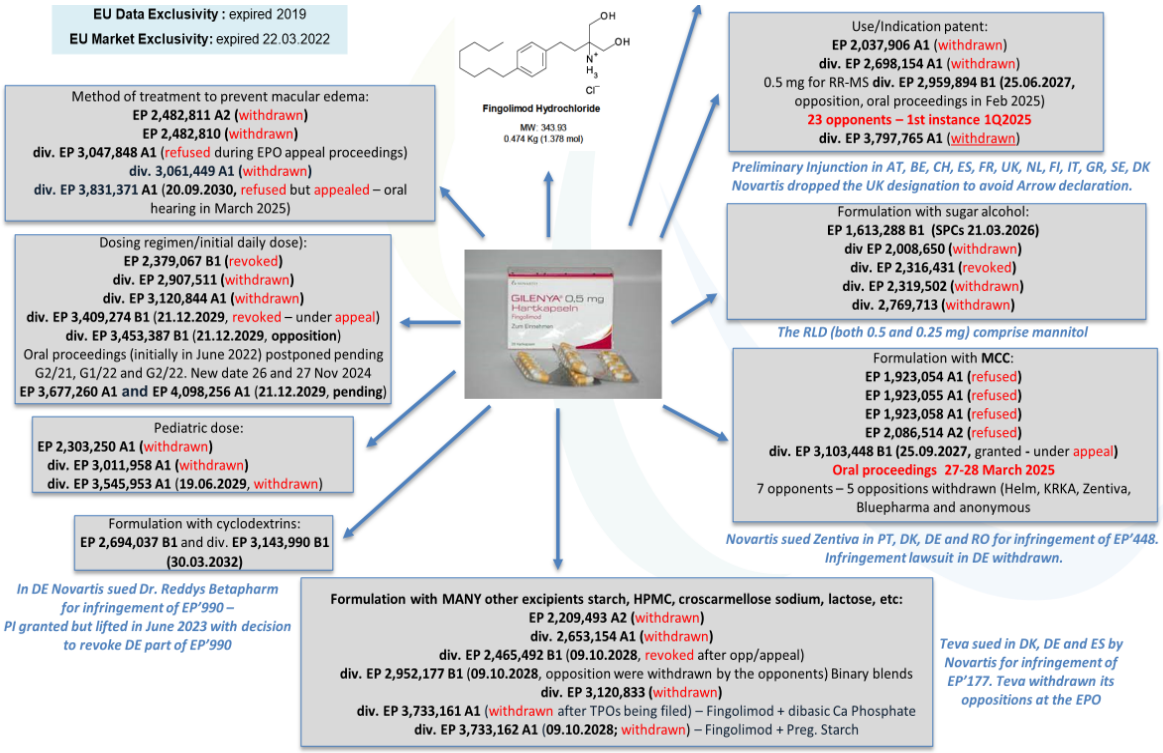
[42] See https://www.medicinesforeurope.com/wp-content/uploads/2022/05/Medicines-for-Europe-letter-to-EC-on-Divisionals-Patent-Linkage-re-Fingolimod-13.04.2022.pdf.
[43] Available here: https://www.medicinesforeurope.com/wp-content/uploads/2022/05/Medicines-for-Europe-letter-to-EC-on-Divisionals-Patent-Linkage-re-Fingolimod-13.04.2022.pdf.

years up to the present time. This delay is most likely to continue until after the EP894 oral proceedings in February 2025 (three years). This patent has been opposed before the European Patent Office by 23 generic companies.

Ultimately, those preliminary injunctions have been overturned or were never granted, for example in the Netherland (October 2022), Germany (July 2023) and Spain (April 2024, where the Appeal Court expressly referred to the "*divisional game*" being used by the company) since the courts considered it likely that the patent will be revoked.

In terms of legal impact, the approximate cost of each opposition and appeal to the European Patent Office would be 80,000 EUR and 40,000 EUR on average, respectively. Those generic companies that launched also bear the costs of defending against the preliminary injunctions (see Section 1.4) in the first and second instances, in the different territories where the generic fingolimod products have been launched. At its peak, the originator company commenced litigation in Denmark, Italy, Sweden, Spain, Belgium, Czechia, Poland, Greece, Germany, Romania, Austria, France, the UK, the Netherlands, Denmark, Switzerland and Finland against more than 25 generic companies. The litigation costs of the generic companies, as a consequence of the originator company's strategy to avoid a timely decision on the validity of this patent, and to aggressively enforce it through preliminary injunctions, are estimated to be in the tens of millions of Euros.

The following diagram shows the patent thicket built by the originator company around its medicinal product Gilenya® capsules (fingolimod):



To conclude, a list of examples of molecules with significant numbers of divisional patents (non-exhaustive) compiled in July 2021 is provided below to give the measure of the issue related to divisional patents. This list shows 182 patents for thirteen medicinal products (among the most relevant ones for generic companies):[44]

OXYCODONE / NALOXONE	62 PATENTS
Parent patent	**Number of patents in family**
EP0576643	15
EP1299104	6
EP0785775	7
EP1492505	7
EP1492506	11
EP1730151	7
EP1897545	9
FINGOLIMOD	**33 PATENTS**
Parent patent	**Number of patents in family**
EP1613288	5
EP2209493	7
EP2379067	7
EP2037906	4
EP2482810	4
EP2086514	3
EP2303250	3
APIXABAN	**7 PATENTS**
Parent patent	**Number of patents in family**
EP2538925	7
BORTEZOMIB	**3 PATENTS**

[44] Table provided by Medicines for Europe.

Parent patent	Number of patents in family
EP1355910	3
LENALIDOMIDE	**7 PATENTS**
Parent patent	**Number of patents in family**
EP1667682	7
APREMILAST	**11 PATENTS**
Parent patent	**Number of patents in family**
EP1485087	9
EP2797581	2
VILDAGLIPTIN	**7 PATENTS**
Parent patent	**Number of patents in family**
EP1715893	5
EP1786401	2
VALSARTAN AMLODIPINE	**3 PATENTS**
Parent patent	**Number of patents in family**
EP1096932	3
CINACALCET	**8 PATENTS**
Parent patent	**Number of patents in family**
EP1663182	8
DIMETHYLFUMARATE	**15 PATENTS**
Parent patent	**Number of patents in family**
EP1799196	6
EP2137537	9
IBRUTINIB	**12 PATENTS**
Parent patent	**Number of patents in family**
EP2081435	12

ABIRATERONE	3 PATENTS
Parent patent	**Number of patents in family**
EP2061561	3
EVEROLIMUS	**11 PATENTS**
Parent patent	**Number of patents in family**
EP1363627	11

1.1.5. India

Divisional patent thickets have been problematic in India, as shown in the table below:[45]

Divisional application filing strategy			Expiry date
	Parent patent	**Divisional**	
Product 1	**Ruxolitinib phosphate (INN)**		
Salt patent application	25KOLNP (parent, appl. Refused U/S 15)	201738033039 (div, abandoned U/S 21(1)	12 June 2028 (refused)
Process patent	2740/KOLNP/2011 (IN 305751, parent-granted)	201838005075 (div-1-IN415604-granted) 201838005065 (div-IN395646-granted) 201838005081 (div-3-IN393617-granted)	14 January 2030
Product 2	**Ceritinib (INN)**		
Product patent-Broad genus	2241/CHENP/2005 (IN232653-parent-granted)	759/CHENP/2009 (div, abandoned U/S 21(1)	12 March 2024
Product patent-species	3951/DELNP/2009 (IN276026-parent-granted)	5338/DELNP/2014 (div)	20 November 2027
Product 3	**Semaglutide (INN)**		

[45] Table provided by IPA.

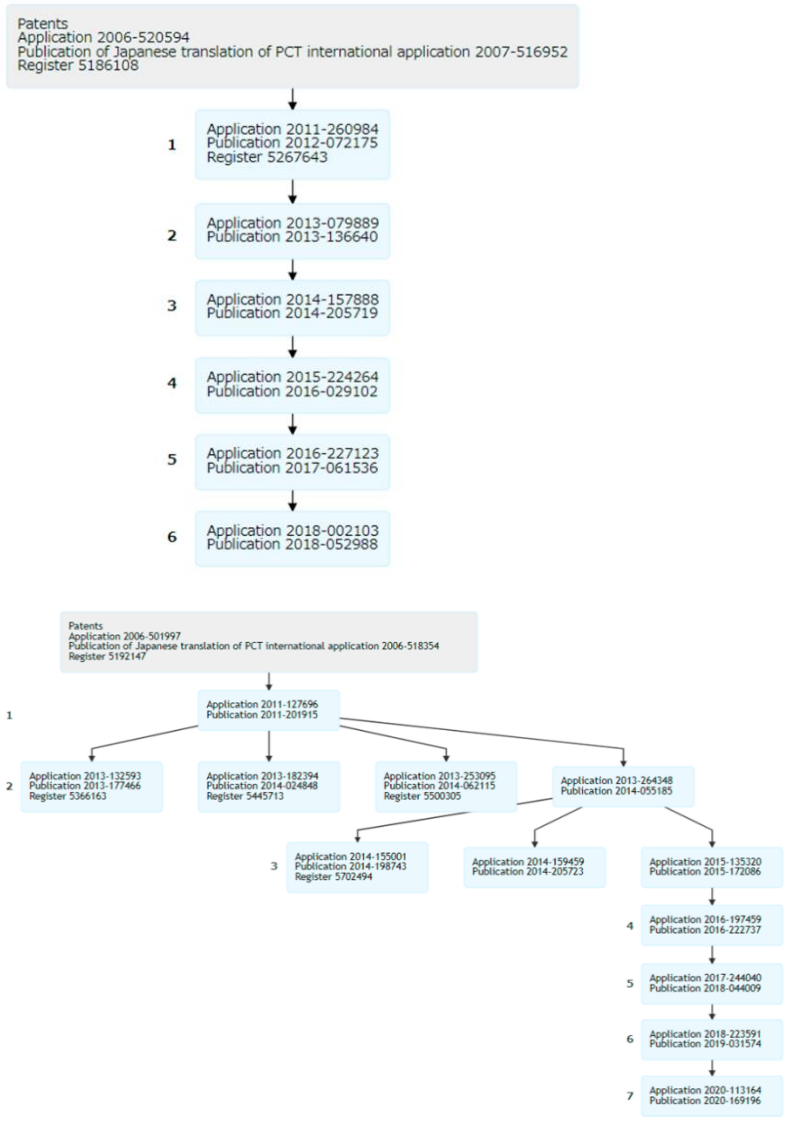
Composition patent	4517/CHENP/2013 (IN325669-granted)	201948047102 (div)	16 December 2031
Composition patent	6970/CHENP/2014 (IN338308-granted)	202048011367 (div)	15 March 2033
Product 4	**Fingolimod (INN)**		
Solid oral composition and process of preparation	2545/CHENP/2005-IN226036	5941/CHENP/2007-div 1-(IN256766-granted) 2425/CHENP/2013-div 2-abandoned	6 April 2024
Product 5	**Apixaban (INN)**		
Product species	590/DELNP/2004-(IN247381-granted)	2092/DELNP/2010-div 1-abandoned 6904/DELNP/2008-div 2-abandoned	17 September 2022
Product 6	**Ibrutinib (INN)**		
Product patent	1642/DELNP/2009-(IN262968-granted)	1575/DELNP/2010-div 1-IN282265 granted 5631/DELNP/2012-div 2-IN362133-granted-claims salt of Ibrutinib	28 December 2026
Swiss type method of use claims	3985/KOLNP/2012-rejected	IN201838043708-div-on combination-refused	3 June 2031 (rejected)

1.1.6. Japan

The impact of the misuse of the patent system by originator companies in Japan has been identified in many cases, such as Livalo® (pitavastatin calcium); Alesion® (epinastine); and, Trazenta® (linagliptin). These cases clearly highlight the impact of patent thickets on the healthcare budgets in Japan.

Livalo® (pitavastatin calcium)

The originator company's medicinal product Livalo® was firstly approved as a tablet containing pitavastatin calcium. Subsequently, the originator company obtained several crystal patents creating the sophisticated divisional tree outlined below.



The last expiry date of the crystal patents is December 17, 2024. According to a press release from the originator company, sales of Livalo® in the year of 2012 were 51 billion JPY.

Generic products were ultimately launched at loss of expiry of the molecule patent. However, the generic companies were sued for infringement, and while the litigated patents were upheld as valid, these were not infringed by the generic companies. As a consequence, due to the significant web of patents around this medicinal product, generic companies incurred significant litigation costs.

Alesion® (epinastine)

The originator company filed several patents covering both benzalkonium chloride-free 0.1% epinastine HCL eye drop and 0.1% epinastine HCL eye drop, comprising benzalkonium chloride protected by several divisionals, creating a significant patent thicket, as illustrated below.

TRAZENTA® (LINAGLIPTIN)

The originator company filed fifteen use patent applications in order to create a patent thicket for linagliptin.[46] As a result, market entry of the generic version of linagliptin will be delayed for at least five years due to the existence of use patent thickets directed to a subpopulation of diabetes patients.

[46] JPB5813293 is directed to dosage of 2.5-10mg one time, which expires on the date of 3 May 2027; JPB6143809 is directed to qd (once a day) dosage regimen, which expires on the date of 3 May 2027; JPB5734564 is directed to combined use of with other anti-diabetes drug, which expires on the date of 3 May 2027; JPB5927146 is directed to combined use of with other anti-diabetes drug, which expires on the date of 3 May 2027; JPB6662970 is directed to heart failure patients, which expires on the date of 3 May 2027; JPB6995822 is directed to the patients with micro vessel complications, which expires on the date of 3 May 2027; JPB6290627 is directed to the patients suffering from moderate to severe and end-stage renal damage, which expires on the date of 5 August 2029; JPB6480887 is directed to the patients suffering from severe chronic kidney disease, which expires on the date of 5 August 2029; JPB6262023 is directed to combined therapy with alpha glucosidase inhibitor, which expires on the date of 15 October

According to the financial statement of the originator company, annual sales of Trazenta® in Japan were about 35.1 billion JPY in 2023. The market entry of a generic version of linagliptin may be delayed for five years from December 2026 to June 2032 due to the use patent thickets.

Based on the assumption that the generic product takes 80% of market volume share, 14.04 billion JPY of national drug expenditure is estimated to be saved in a year.

1.1.7. Middle East and North Africa

The use of patent thickets and the misuse of the divisional patents also take place in the Middle East and North Africa, as clearly identified for Kerendia® (finerenone); Gilenya® (fingolimod); and, Imbruvic® (ibrutinib).

Kerendia® (finerenone)

Finerenone is sold under the brand name Kerendia® by the originator company for the treatment of chronic kidney disease. The reference product was approved in the U.S. in 2021, and the Food and Drug Administration considers it to be "a first-in-class medication". This medicinal product is protected by eleven patents/patent applications in Jordan.[47]

Gilenya® (fingolimod)

Fingolimod is sold under the name Gilenya® by the originator company for treatment of relapsing forms of multiple sclerosis. The originator company filed nine patents in Algeria.[48]

Imbruvic® (ibrutinib)

Ibrutinib is sold under the brand name Imbruvic® by the originator company for the treatment of different kinds of cancers. There are four divisional patent applications filed for the same invention in the patent office, creating significant legal uncertainty; the first application was granted in 2018 with patent number GC8085 and revoked in 2022 based on the decision of the grievance committee after opposition, another patent application was rejected technically by the patent office of the Gulf Cooperation Council and it is still under appeal, and the other two patent applications are still under examination. The last application was filed in 2022.

2029; JPB6811203 is directed to the patients who did not respond to neither metformin nor insulin, which expires on the date of 15 October 2029; JPB7174020 is directed to the patients who did not respond to sulfonylurea, which expires on the date of 15 October 2029; JPB6556767 is directed to various combined therapy with various other anti-diabetes medicines, which expires on the date of 12 February 2030; JPB6189374 is directed to combined therapy with long-acting insulin for the elder patients, which expires on the date of 22 June 2031; JPB7227107 is directed to the patient with cardiovascular risk factor, which expires on the date of 15 November 2031; JPB6342435 is directed to prevention of cardiovascular event or cerebrovascular event, which expires on the date of 15 November 2031.

[47] Product patent, WO2008104306, (JO 80/2008 (3018)), Exp. date. 26-Feb-2028; Process patent, WO2016016287, (JO 184/2015 (3648)), Exp. date. 30-Jul-2035; Process patent, WO2017032673, (JO 186/2016 (3844)), Exp. date. 18-Aug-2036; Process patent, WO2017032678, (JO 185/2016 (3843)), Exp. date. 18-Aug-2036; Process application, WO2019206909, (JO 2020/0267), Exp. date. 23-Apr-2039; Process application, WO2020178175, (JO 2021/0242), Exp. date. 28-Feb-2040; Process application, WO2020178177, (JO 2021/0243), Exp. date. 28-Feb-2040; Process application, WO2021074072, (JO 2022/0091), Exp. date. 12-Oct-2040; Process application, WO2021074077, (JO 2022/0148), Exp. date. 12-Oct-2040; Process application, WO2021074078, (JO 2022/0089), Exp. date. 12-Oct-2040; Process application, WO2021074079, (JO 2022/0090), Exp. date. 12-Oct-2040.

[48] Including: DZ4313 with Exp. date: 06- Apr-2024; DZ7016 with Exp. date: 09-Oct-2028 and DZ130676 with Exp. date: 30-Mar-2032.

1.1.8. South Africa

The misuse of the patent system and its impact on the pricing of medicinal products in South Africa can be illustrated in the context of Sirturo® (bedaquiline).

Sirturo® (bedaquiline)

The Competition Commission, in July 2024, concluded an investigation in the context of a medicinal product used to treat tuberculosis. The Competition Commission investigated two originator companies following allegations of abuse of dominance after the companies filed a secondary patent for Sirturo® (bedaquiline), effectively restricting the entry of generic products. After extensive engagement with the originator companies, the Competition Commission eventually decided not to refer the complaint to the Competition Tribunal for prosecution and the companies, in turn, agreed not to enforce the bedaquiline patent in 134 low-and middle-income countries, including South Africa, opening the market allowing for the entry of generic companies.

In addition, the originator companies renegotiated the prices of Sirturo® they charged the National Department of Health. Accordingly, the price of the medicinal product was reduced by approximately 40% from 5,577.12 ZAR to 3,148.00 ZAR.[49]

1.1.9. United Kingdom

The misuse of the divisional patent system takes place in the United Kingdom. An early, striking case relates to the originator company's high-revenue osteoporosis medicinal product Fosamax® (alendronate).

FOSAMAX® (ALENDRONATE) – Divisional game and product hopping

The basic patent on the active ingredient alendronate had been invalidated in most European jurisdictions. After that patent was revoked in the United Kingdom, several claims of another patent (EP 402 152) were voluntarily abandoned in various countries.[50] There was, however, another patent family related to the use of alendronate for the treatment of the bone disease osteoporosis according to a certain dosage regime. The parent patent, EP 998 292, was both successfully opposed before the European Patent Office and revoked in a number of European jurisdictions. Nevertheless, the patentee filed four substantially identical divisional applications, including EP 1 175 904 (for a 70 mg once weekly dosage regime), which was granted. The originator company subsequently sought to enforce it to prevent the commercialisation of a generic version of alendronate 70 mg (despite the revocation of the parent patent and seventeen pending oppositions before the European Patent Office against the divisional patent). Also, the Dutch and Belgian courts concluded that EP 1 175 904 was invalid.

It should be noted that in the meantime the originator company used its marketing resources to shift the market from Fosamax® to Fosavance®, which is the same medicinal product as Fosamax® with the addition of a small amount of vitamin D.[51] This "new" medicinal product, with no substantial added therapeutic value, was

[49] See: https://www.compcom.co.za/wp-content/uploads/2024/07/TUBERCULOSIS-PATENT-COMPLAINT-AGAINST-JOHNSON-JOHNSON.pdf.
[50] Arrow v Merck [2007] EWHC 1900 (Pat).
[51] Such practice, defined as product hopping, is described in Chapter 2.1.

even the subject of a patent application despite the fact that patients who were prescribed Fosamax® in the past were instructed to consume this medicinal product in combination with vitamin D.

As a result, generic companies had to sustain huge opposition and litigation costs in the face of a clear evergreening strategy put in place by the originator company combining patent thickets with product hopping (see Section 3.1).

The misuse of the divisional patent system was also clearly identified by the UK courts in the case concerning Humira® (adalimumab). In this regard, Richard Gonzalez, CEO of the originator company, publicly stressed that Humira® had 70 additional ancillary patents covering formulation, manufacture and dosage expiring between 2022 and 2034: "*Any company seeking to market a biosimilar version of Humira® will have to contend with [our] extensive patent estate, which [our originator company] intends to enforce vigorously. We believe the litigation process and our intellectual property estate will protect Humira from biosimilar entry until 2022.*"[52]

Humira® (adalimumab)

The originator company owned several patents related to adalimumab, a treatment for conditions like rheumatoid arthritis, psoriatic arthritis, and psoriasis. Prior to biosimilar launch, Humira® was one of the highest-selling prescription medicinal products globally, with sales of around 20 billion USD in 2018.

Biosimilar companies intended to market adalimumab medicinal products in the UK, after the expiry of the originator company's basic adalimumab patent and its associated supplementary protection certificates in October 2018. They sought declarations that their products were not infringing in the UK. The originator company attempted to avoid trial in the UK by applying for summary judgment or to have the proceedings struck out as an abuse of process. The originator company also engaged in practices such as de-designating the UK from certain patents.

The court dismissed the originator company's applications and found that there was a real prospect that the trial judge would grant the generic companies' non-infringement declarations.[53] This included the originator company's strategy of "*threatening infringement whilst abandoning proceedings at the last moment (in order to shield its patent portfolio from scrutiny)*", therefore "*dragging out proceedings for as long as possible, causing maximum expense and inconvenience to its opponents, and then throwing in the towel just before its patents are scrutinised by the court*".[54]

On October 16, 2018, the compound patent/supplementary protection certificate for Humira® came to an end in most European countries and the United Kingdom. However, secondary patents for dosage regimens for rheumatoid arthritis and inflammatory bowel disease were still active in the European Union and in the United Kingdom. To address this legal uncertainty, biosimilar companies started several litigation cases against the originator company for these secondary patents, and opposed those patents at the European Patent Office. Eventually multiple companies with a biosimilar adalimumab reached a settlement agreement in which biosimilars were allowed to launch in October 2018 without any risk of litigation, and an undisclosed royalty

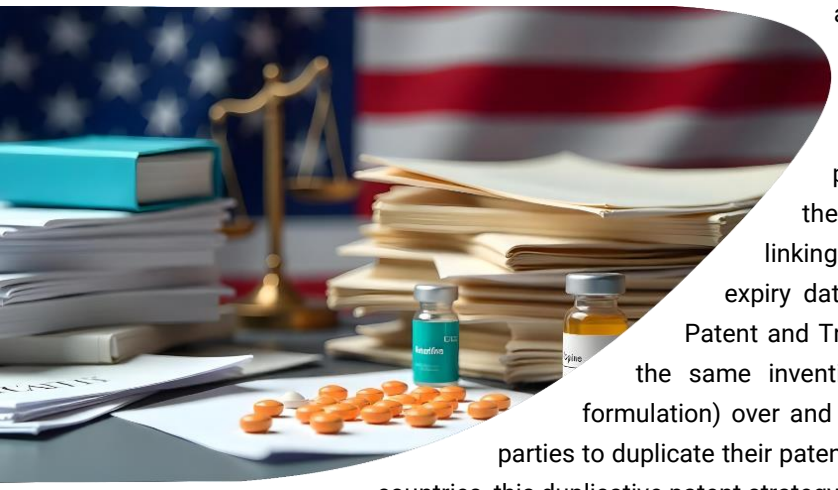
[52] BiopharmaReporter.com, 3 Nov 2015.
[53] [2016] EWHC 3383 (Ch), para. 44.
[54] [2017] EWHC 395 (Pat)., para 416 and 357.

agreement. In other words, the biosimilar companies would each pay royalties to the originator company for a non-exclusive licensing agreement on European patents related to Humira® starting from October 16, 2018, depending on the company-specific arrangements.

Therefore, while European competition could occur on a timely basis, biosimilar companies were forced through lengthy and costly litigation[55], including: (i) oppositions to ten patents with up to fifteen opponents each at the European Patent Office. Even if those oppositions were only 50,000 EUR each, that represents over 3.5 million EUR in legal fees wasted to resolve the patent risk on patent that ultimately did not delay launch[56]; and (ii) national litigation in the UK, which can be up to several million EUR.[57]

1.1.10. United States

In the United States, market entry of generic and biosimilar products can be delayed by expansive patent thickets, which are dozens or hundreds of patents directed to the same medicinal product. One way that originator companies build patent thickets is through a special type of patent application to the U.S. Patent and Trademark Office called a "continuation". Continuation patents typically arise in patent families directed to minor follow-on innovations, such as new methods of treatment or modified formulations. Many continuation patents are initially rejected by the patent office for being "non-patentably distinct", i.e. obvious variants over other patents belonging to the same patent owner. However, the patent owner can overcome these rejections by linking their continuation patents together with a common expiry date, called a terminal disclaimer. Therefore, the U.S. Patent and Trademark Office permits parties to effectively patent the same invention (i.e. the same dosing regimen or the same formulation) over and over again. The U.S. is the only country that allows parties to duplicate their patents using this terminal disclaimer manoeuvre. In other countries, this duplicative patent strategy is known as "double patenting" and is not permitted.



In the U.S., patent thickets create uncertainty for generic and biosimilar companies who must avoid or invalidate every claim of every patent to enter the market, which becomes a cost-prohibitive proposition as the number of patents increases. Generic and biosimilar companies routinely challenge low-quality, secondary patents as a means to come to the market sooner, but the existence of so many duplicative patents is troublesome. While patents may cost as little as 25,000 USD to obtain, on average it costs 774,000 USD to challenge a patent in an *inter partes* review or post-grant review. Federal court litigation is even more expensive, ranging into the 10s of millions USD. Furthermore, it seems unlikely that a court can effectively litigate scores of patents which may lead to shielding low-quality patents from scrutiny. Originator companies know that it is a numbers game that biosimilar companies

[55] E. Moorkens, e.a., "The Expiry of Humira® Market Exclusivity and the Entry of Adalimumab Biosimilars in Europe: An Overview of Pricing and National Policy Measures" 11(2021) Frontiers in Pharmacology, 1 - 17.
[56] IPD Analytics extract, 12 July 2024 showing opposition details for EP1405565, EP1528933, EP1737491, EP1941904, EP1944322, EP2350127, EP2637690, EP2822591, EP2940044, EP3021833.
[57] https://www.legal500.com/guides/chapter/united-kingdom-patent-litigation/.

cannot win. The result is delayed launches which keep patients and the Medicare program paying significantly higher costs for medicinal products.

On September 10, 2021, the Commissioner of the Food and Drug Administration sent a letter to the Director of the U.S. Patent and Trademark Office stressing the issues of patent thickets, abuses of continuation patents, product hopping and evergreening.[58] This triggered a formal collaboration between the Food and Drug Administration and the U.S. Patent and Trademark Office to prevent the grant of non-innovative patents.[59] This is of crucial importance because similar political pressure on patent offices is needed in other jurisdictions.

On March 24, 2023, the Director of the U.S. Patent and Trademark Office, Kathy Vidal, received a letter[60] from a bipartisan group of Members of Congress, namely Jodey Arrington, Michael Burgess, Lloyd Doggett, Darrell Issa and Ann McLane Kuster. The members urged Vidal to consider rule changes to address the issues of duplicative patent thicket practices in the pharmaceutical space. The letter included the following example of two patents covering a blockbuster drug that claim non-distinct inventions: (i) claims to a method of treating rheumatoid arthritis in a human subject using a particular dosage regimen; and (ii) claims to a method of reducing signs and symptoms [of rheumatoid arthritis] in a patient using the exact same dosage regimen.[61] As can be seen from this example, the only difference in scope between these patents is the term "human subject" versus "patient" and the "treatment" of rheumatoid arthritis versus "reducing signs and symptoms" of rheumatoid arthritis.

On January 4, 2024, Representative Jodey Arrington (TX-19) led a bipartisan, bicameral group of lawmakers, including Representatives Doggett, Pfluger, Dingell, Issa and Jayapal and Senators Braun and Welch in introducing a bill to lower prescription medicinal products costs by addressing patent thickets.[62] The bill prevents originator companies from asserting more than one patent from a group of patents that are linked together through terminal disclaimers.[63] In other words, only one patent per distinct invention would be litigated. The bill is supported by peer review data showing that in some cases as much as 80% of a medicinal product's patent portfolio is terminally disclaimed (i.e. duplicative).[64]

On May 9, 2024, the U.S. Patent and Trademark Office issued a notice proposing a new rule that would "add a new requirement for terminal disclaimers filed to obviate (overcome) non-statutory double patenting".[65] The proposed rule change would require terminal disclaimers to include an agreement by the patent applicant that they will not enforce the patent if any claim of the terminally disclaimed patent has been finally held unpatentable or invalid. In other words, generic or biosimilar companies would only have to invalidate a single claim in a patent, and all other patents tied to it through terminal disclaimers would become non-enforceable. **The International Generic and Biosimilar Medicines Association (IGBA) supports the proposal**.

The patent thicket problem is exasperated by the issue of standing. Generic and biosimilar companies do not have standing, that is the right to challenge patents in Federal Court, until their dossier is on file with the Food and Drug Administration. Patent litigation can take approximately three to five years to reach a final non-appealable decision,

[58] See https://www.fda.gov/media/152086/download.
[59] https://www.fda.gov/about-fda/reports/fda-uspto-collaboration-initiatives.
[60] Letter from the Acting Commissioner of Food and Drugs to Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office. September 10, 2021. Retrievable at: https://www.fda.gov/media/152086/download.
[61] See https://arrington.house.gov/uploadedfiles/2023_03_024_arrington_letter_uspto_director_vidal.pdf at 1.
[62] See https://arrington.house.gov/news/documentsingle.aspx?DocumentID=1174.
[63] See https://www.govinfo.gov/content/pkg/BILLS-118s3583is/pdf/BILLS-118s3583is.pdf.
[64] Rachel Goode, Bernard Chao, Biological patent thickets and delayed access to biosimilars, an American problem, Journal of Law and the Biosciences, Volume 9, Issue 2, July-December 2022, lsac022, https://doi.org/10.1093/jlb/lsac022 Add to Citavi project by DOI; Tu SS, Goode R, Feldman WB. Biologic Patent Thickets and Terminal Disclaimers. JAMA. 2024 Jan 23;331(4):355-357. doi: 10.1001/jama.2023.25389. PMID: 38095894; PMCID: PMC10722383.
[65] See https://www.federalregister.gov/documents/2024/05/10/2024-10166/terminal-disclaimer-practice-to-obviate-nonstatutory-double-patenting.

whereas the Food and Drug Administration review takes only twelve months. Therefore, generic and biosimilar companies tend to obtain approval of the Food and Drug Administration at a time when the court litigation is just getting started. They then face the choice of voluntarily delaying their launch while waiting for a final resolution from the court or launching “at risk” before a decision on any relevant patents. This is an intimidating predicament because the consequence of being found to infringe a valid patent includes an injunction or an order to pay the lost profits of the originator company, which can run into hundreds of millions of USD.

The timing of when a patent can be challenged due to standing is more harmful for biosimilar products than generic products. In both cases, companies typically target to launch upon expiry of the product patent, which is usually considered to be the strongest patent in the portfolio and is typically the first patent to expire. Litigation serves to resolve the validity and infringement of the follow-on patents, i.e. those patents that were filed later than, and expire later than, the basic product patent. As explained above, development of a generic product takes approximately three years, meaning that generic companies submit their dossier to the Food and Drug Administration and obtain standing to litigate the patents in ample time before the product patent expires. In other words, generic companies in some cases may have sufficient time to litigate the follow-on patents to a final resolution prior to their target launch date. However, the development of a biosimilar product currently takes much longer (over eight years) meaning that clarity on the patent risk is also delayed. The long development time for biosimilar products provides time for originator companies to build up their patent portfolios and grow excessively large patent thickets, which can go un-checked until a biosimilar company completes the development of the biosimilar product. As of today, no biosimilar company has been able to litigate their case to a final decision prior to product patent expiry (the target launch date).

Delayed access to court resolution often leads to patent settlements, which are an agreement between the originator company and the generic or biosimilar company that provides the generic or biosimilar company with a license to the patents. Parties enter into a settlement to resolve uncertainty. Many patent settlements include fixed market entry dates that permit generic or biosimilar companies to launch their product, typically later than the expiry of the basic product patent. The larger the patent thicket, the greater the uncertainty, and the greater the leverage that the originator company has over the generic or biosimilar company in settlement negotiations to insist on later market entry dates.

On September 13, 2023, Senators Hassan, Braun and Representatives Kuster, Harshbarger introduced a bipartisan bill "The Medication Affordability and Patent Integrity Act" which would require originator companies to certify that they have not made inconsistent statements to the U.S. Patent and Trademark Office as compared to the Food and Drug Administration. One example of an inconsistent statement is where an originator company tells the Food and Drug Administration that a modification to the purity level of the medicinal product has no impact on potency and safety, and on the other hand they inform the U.S. Patent and Trademark Office that the new purity level is advantageous and worthy of patent protection. This bill goes towards ensuring that the same medicinal product is

not patented more than once, for example where the first patent describes the chemical structure of the medicinal product and the second patent describes an ancillary feature of the medicinal product, such as its purity level. Generic and biosimilar companies applaud and support these measures, but Congress needs to do more, in particular, with respect to the issue of delayed standing to challenge the patents in Federal Court.

In this context of the misuse of the patent system, Congress has brought specific attention to an originator company's patenting practices with respect to the cancer medicinal product Keytruda® (pembrolizumab).

Keytruda® (pembrolizumab)

Keytruda® (pembrolizumab) is an expensive and important anticancer medicinal product, which costs around 165,000 USD per year of treatment. To extend its monopoly and continue making profits, as of October 2021, the originator company filed for 129 patents, with many more expected.[66]

If this patent thicket has the same effect on the timing of biosimilar products as a similar thicket created for Humira® (adalimumab), which is discussed in more details below, it could delay the launch of biosimilar products of pembrolizumab for several years after the expiration of these patents. The annual sales of Keytruda® increased by nearly 20% to approximately 25 billion USD in 2023 and are forecast to top 30 billion USD by 2026, so any delay to the launch of biosimilar products will have a massive impact on the healthcare system in the United States.[67]

The misuse of the patent system was also clearly identified in the case concerning Humira® (adalimumab). This case clearly underlines originator companies' strategy to create patent thickets in order to increase the costs of medicinal products and to create barriers to biosimilar companies to enter the market.

Humira® (adalimumab)

The biologic Humira® became a more lucrative franchise than the entire National Football League.[68] The prolonged high price of this much-in-demand medicinal product is a direct function of the current U.S. patent system, which has allowed the originator company to obtain approximately 136 patents that stack exclusivity period on top of exclusivity period — far more than the "limited" exclusivity period contemplated by the Constitution.[69] From the time the key patent on Humira® was set to expire in 2016, the originator company has raised the medicinal product's list price by 60%, generating an additional 114 billion USD in revenue for the company.[70] The originator company's clear intent was to accumulate patents because they increased costs and constitute barriers for potential biosimilar companies. Indeed, external, peer-reviewed research has found

[66] See https://www.warren.senate.gov/imo/media/doc/2023.02.22%20Letter%20to%20USPTO%20re%20Keytruda%20patent1.pdf at 1.
[67] Reuters: https://www.reuters.com/business/healthcare-pharmaceuticals/merck-posts-better-than-expected-quarterly-results-soaring-keytruda-sales-2024-02-01/.
[68] See Budwell, Can You Guess What Legal Drug Outsells The NFL?, The Motley Fool, Jan 31, 2015, available at https://www.fool.com/investing/general/2015/01/31/can-you-guess-what-legal-drug-outsells-the-nfl-hin.aspx.
[69] See Hagen, Alvotech Files Suit to Invalidate Humira Patents, AJMC, May 11, 2021, available at https://www.centerforbiosimilars.com/view/alvotech-files-suit-to-invalidate-humira-patents; U.S. Const. art. 1, § 9, cl. 9 ("[The Congress shall have Power . . .] To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.").
[70] See Robbins, How a Drug Company Made $114 Billion by Gaming the U.S. Patent System, The New York Times, Jan 28, 2023, available at https://www.nytimes.com/2023/01/28/business/humira-abbvie-monopoly.html.

that the Humira® patent estate is comprised of 80% duplicative patents.[71] This practice is entirely allowed by rules of the Patent and Trademark Office rules. And this is not merely a Humira® problem: numerous other large originator companies are purportedly following this exact same strategy.[72]

The originator company commenced a number of patent litigations in the U.S. against various biosimilar companies. All of the suits were settled under terms permitting biosimilar market entry in 2023.[73] Following those settlements, indirect purchasers alleged violations of both Sections 1 and 2 of the Sherman Antitrust Act. Most notably with regard to the issue of "patent thickets", the purchasers alleged that the sheer number of patents the originator company obtained for Humira® and asserted in litigation amounted to a violation of Section 2 of the Sherman Act. The indirect purchasers' complaint asserted that biosimilar companies could have — and should have — begun on January 1, 2017, rather than in 2023, but was delayed by the originator company's patent thicket. It also alleged that the originator company's 9.7% price hike in 2018 alone cost the U.S. healthcare system approximately 1.2 billion USD.[74]

The District Court responded by dismissing the complaint, and the Seventh Circuit affirmed the dismissal. In reaching its conclusion, the Seventh Circuit stated: "*But what's wrong with having lots of patents? If [the originator company] made 132 inventions, why can't it hold 132 patents? The patent laws do not set a cap on the number of patents any one person can hold—in general, or pertaining to a single subject*."[75]

The court continued by noting that invalid patents cannot protect a monopoly, but in this particular case, the plaintiffs did not offer to prove that all of the 132 patents in question were invalid or inapplicable, and thus, plaintiffs were not able to sufficiently plead their cause that the delay in market entry was improper.[76] The court's dismissal does not address a principal practical concern of patent thickets, i.e. that the sheer existence of 132 patents makes it prohibitively expensive and time consuming (as well as unreasonably burdensome for the judiciary) to dispose of a litigation involving such a huge number of duplicative patents, other than to say the U.S. system does not limit the number of patents obtained.[77] It also does not address the fact that there were not in fact 132 inventions comprised by those 132 patents.

The economics of these litigations are also very different for an originator company, who can offset the cost of the litigation against the often sizable revenues and profits earned from every additional day of market exclusivity for a specific medicinal product. In contrast, a biosimilar company endeavouring to get its medicinal product to market must absorb the cost of the litigation in the hope that the court will permit a launch that is timely and profitable enough to recoup the cost.

In addition to the above examples, several cases clearly identify the implications of patent thickets on the market entry of generic and biosimilar companies in the United States, the huge reduction in healthcare savings, as well as

[71] See Rachel Goode & Bernard Chao, Biological Patent Thickets and Delayed Access to Biosimilars, J.L & Biosciences 1, 19 (2022) available at https://doi.org/10.1093/jlb/lsac022.
[72] See https://www.warren.senate.gov/imo/media/doc/2023.02.22%20Letter%20to%20USPTO%20re%20Keytruda%20patent1.pdf (alleging that Merck's efforts to extend its patent monopoly "appear to be part of a long-standing pattern of drug manufacturers' abuse of the patent system"); Big Pharma's Patent Abuses are Fueling the Drug Pricing Crisis. Tahir Amin and David Mitchell https://time.com/6257866/big-pharma-patent-abusedrug-pricing-crisis/ (referring to Regeneron's Eylea product as "a perfect poster child for undeserving patents").
[73] Mayor and City Council of Baltimore v. Abbvie Inc., 42 F.4th 709, 714 (7th Cir. 2022).
[74] See UFCW Local 1500 Welfare Fund v. Abbvie Inc. et al., 19-cv-01873, Docket Entry 1 at 19-20.
[75] See Mayor and City Council of Baltimore at 714.
[76] See id. at 713-714.
[77] See id. at 714.

the significant litigation implications involved. These cases relate, amongst others, to Latisse® (bimatoprost); Hetlioz® (tasimelteon); Myrbetriq® (mirabegron); Combigan® (brimonidine/timolol).

Latisse® (bimatoprost)

In 2011, Sandoz and Apotex filed an abbreviated new drug application for bimatoprost, challenging two patents the originator company listed in the Orange Book in connection to its branded bimatoprost product, Latisse®. One of those patents was U.S. Patent No. 7,388,029 (the "'029 patent"). In 2014, the Federal Circuit determined the '029 patent was invalid for obviousness.[78]

The originator company obtained other patents related to the '029 patent and again sued Sandoz for infringement in 2014. The originator company voluntarily dismissed one action in the district court after the Federal Circuit decision invalidating the '029 patent, and the Federal Circuit later affirmed a district court's application of collateral estoppel on the issue of claim construction in the other.[79]

Shortly after the Federal Circuit invalidated the '029 patent, the originator company filed another application in 2015 that claimed priority to the '029 patent. The application claims were substantially similar to the '029 patent claims. So, when faced with an obviousness-type double patenting rejection in that application, rather than argue in the patent office that its new claims were patentably distinct, the originator company filed a terminal disclaimer to secure issuance of a follow-on patent, U.S. Patent No. 9,579,270 (the "'270 patent), which issued in 2017.

As soon as the '270 patent issued, the originator company attempted yet another bite at the apple, suing Sandoz for infringement in a different jurisdiction, the Eastern District of Texas, this time seeking a jury trial and damages, as Sandoz had already launched its generic bimatoprost product after invalidating the previously asserted '029 patent. Because of the terminal disclaimer, Sandoz could not raise double patenting as a defense. On its fourth attempt, the originator company succeeded in convincing a jury that the '270 patent was valid and obtained a damages award of 39,000,000 USD. It did so in part by excluding evidence of the previous revocation of the '029 patent from the jury.

Sandoz is appealing this decision, but even if successful, the litigation costs on the product through four rounds of litigation would have supported the development of three or four new generic products.

Hetlioz® (tasimelteon)

Patent litigation began on tasimelteon in 2018, when the originator company filed patent infringement lawsuits in Delaware against Teva, MSN, and Apotex, asserting six patents related to the use of tasimelteon to treat a sleep disorder. During the pendency of the litigation, the originator company added six more related patents, some terminally disclaimed to the originally asserted patents, resulting in multiple postponements of the trial date. The serial addition of patents became so abusive that the Delaware Court finally asked the originator company to agree not to assert any more patents on this medicinal product.[80] The originator company agreed.

[78] Allergan, Inc. v. Apotex Inc., 754 F.3d 952, 963 (Fed. Cir. 2014).
[79] See Allergan, Inc. v. Sandoz, Inc., 681 F. App'x 955, 962 (Fed. Cir. 2017).
[80] Vanda Pharms. Inc. v. Teva Pharms. USA, Inc., 2023 WL 1883357, at *1 n.2 (D.N.J. Feb. 10, 2023).

Trial finally took place in 2022 against Teva and Apotex, resulting in the court finding the four patents that remained in the case invalid for obviousness.[81] The Federal Circuit denied an injunction pending appeal in December 2022, and both Teva and Apotex launched their medicinal products. In May 2023, the Federal Circuit affirmed the district court's decision.[82]

Meanwhile, notwithstanding its agreement not to assert any more patents, in a clear effort at forum shopping, the originator company filed complaints against Teva and Apotex in the District of New Jersey and the Southern District of Florida, asserting a newly issued patent, U.S. Patent No. 11,285,129, which is directly related to the patents-in-suit that were found invalid. The Florida case was ultimately dismissed, and the New Jersey case was transferred back to Delaware and is currently pending there. Teva and Apotex now face the same risk in a jury trial as Sandoz did with bimatoprost.

There are currently 30 patents listed in the Orange Book for tasimelteon, many of which are newly issued and yet to be asserted—for a medicinal product that was first approved ten years ago. All of the newer patents are related to the older ones, and several are tied with terminal disclaimers to the patents invalidated in the Federal Circuit.

The originator company has every reason to continue its serial filing of patent applications, hoping to find one form of claim that will survive an invalidity challenge and cover its generic competitors. After all, it has avoided the scrutiny of the patent office on multiple occasions, simply by filing a terminal disclaimer. Indeed, that the originator company decided to file a follow-on litigation on only one patent of the many it has obtained suggests that it may be holding the remaining patents as a threat to follow if the originator company fails on the latest challenge.

Myrbetriq® (mirabegron)

In 2016, nine generic companies, including Sandoz, Lupin, and Zydus, filed abbreviated new drug applications seeking FDA approval for generic mirabegron (Myrbetriq®). The originator company sued all nine abbreviated new drug application filers in the District of Delaware, asserting up to five patents related to the compound, polymorphic forms, and methods of treatment, against each filer. Before trial, the originator company settled all the cases for a date-certain launch.[83] All but two generic filers have not launched their generic products, and eight years later, the originator company continues to pursue serial litigation against the two companies that persisted in their patent challenges.

A mere few months after the settlements resolving the first litigation were signed, the originator company sued all nine filers a second time on the same medicinal product, this time asserting infringement of a formulation patent, U.S. Patent No. 10,842,780 (the "'780 patent"). All but three filers — Lupin, Sandoz, and Zydus — settled the second case. In 2023, after trial in the second round of litigation, the district court held the '780 patent invalid for claiming ineligible subject matter in violation of 35 U.S.C. § 101. That decision is currently on appeal.[84]

[81] Vanda Pharms., Inc. v. Teva Pharms. USA, Inc., 2022 WL 17593282, at *27–28 (D. Del. Dec. 13, 2022), aff'd, 2023 WL 3335538 (Fed. Cir. May 10, 2023), cert. denied, 144 S. Ct. 1393 (2024).
[82] Vanda Pharms. Inc. v. Teva Pharms. USA, Inc., 2023 WL 3335538, at *1 (Fed. Cir. May 10, 2023), cert. denied, 144 S. Ct. 1393 (2024).
[83] Report and Recommendations at 6, Astellas Pharma Inc. v. Lupin Ltd., No. 1:23-cv-00819 (D. Del. April 19, 2024), ECF No. 200.
[84] Ibid.

While the '780 patent was in litigation, the originator company was prosecuting a second formulation patent application in that same family. The examiner rejected this application for, among other reasons, obviousness-type double patenting over the '780 formulation patent because the claims "*are not patentably distinct from each other*". The examiner elaborated that the claims are directed to the same subject matter: a "sustained release formulation" containing mirabegron. In response, rather than attempting to distinguish its new claims from the '780 patent claims, the originator company filed a terminal disclaimer. The second formulation patent issued shortly thereafter, as U.S. Patent No. 11,707,451 (the "'451 patent").

In July 2023, the originator company asserted the '451 patent in a third round of litigation against Lupin, Zydus, and Sandoz, again in the District of Delaware. With this new round of litigation on the same medicinal product, Sandoz entered into a patent settlement, rather than continuing to challenge this patent family.

While Lupin and Zydus launched their medicinal products at risk shortly after defeating a preliminary injunction by the originator company, separate litigations on the '451 patent and the '780 patent are ongoing. The originator company also continues to prosecute further patent applications on Myrbetriq® and it remains to be seen if additional waves of litigation will occur.

As with bimatoprost, the originator company was able to serially litigate multiple waves of patents with minor variations, tweaking its claims each time with a slightly different approach, to see what claim scope would win in litigation. Under the current terminal disclaimer practice, the originator company avoided the U.S. Patent and Trademark Office's substantive review of these claims for double patenting by filing terminal disclaimers — without incurring any consequences on its ability to enforce multiple indistinct variations of its claims in serial litigation against the same generic competitors.

And like in the bimatoprost litigation, the abbreviated new drug application filers who launched at risk are exposed to the risk of patent damages. To eliminate the current risk of damages, Lupin and Zydus will need to prevail in at least two separate litigations and potentially before two different factfinders. And what will they do if another child application terminally disclaimed to the '780 patent issues as a third formulation patent and is asserted in a fourth round of litigation? That risk is calculated to disincentivize generic competition.

Combigan® (brimonidine/timolol)

This case involves at least three separate waves of litigation by the originator company over a thirteen-year period on a combination product, brimonidine/timolol, that began in 2009.

In the first wave of litigation, the originator company asserted multiple patents directed to the combination of brimonidine and timolol against Sandoz and several other generic filers, including Apotex and Watson. The Federal Circuit found the asserted claims of US Patent No. 7,323,463 (the "'463 patent") obvious in 2013.[85]

After the Federal Circuit's invalidity opinion, the originator company obtained U.S. Patent No. 8,748,425 (the "'425 patent"). Rather than convincing the U.S. Patent and Trademark Office that the '425 patent's claims were patentably distinct, it did so by filing a terminal disclaimer against the earlier asserted patents, including the invalidated '463 patent. In a second wave of litigation, the originator company asserted the '425 patent, among others, against Sandoz and the other filers. Both Apotex and Watson entered into settlements with the originator company during the second wave of litigation, but Sandoz continued to litigate in an effort to bring its generic product to market. In December 2016, the district court found that Sandoz infringed the '425 patent

[85] Allergan, Inc. v. Sandoz Inc., 726 F.3d 1286, 1294 (Fed. Cir. 2013).

but did not infringe any other asserted patent.[86] The Federal Circuit reversed that finding in 2017, ruling that Sandoz did not infringe the '425 patent, but, this time, it did not find the patent invalid.[87]

The originator company then pursued yet another wave of litigation against Sandoz, including on U.S. Patent Nos. 9,770,453, 9,907,801, and 9,907,802, patents that were terminally disclaimed to, among other patents, the invalidated '463 patent. The originator company conceded in its complaint that these patents were obtained specifically to ensure that the claims covered Sandoz's proposed product.[88] In July 2018, on its third bite at the apple, this time in a different jurisdiction, the originator company was able to secure a preliminary injunction preventing Sandoz from launching its generic product.[89] In 2022, Sandoz, too, entered into a patent settlement.

The terminal disclaimer rules again allowed the originator the opportunity to repeatedly redraft its claims until it was able to capture Sandoz's medicinal product. Instead of the validity and scope of the patent being resolved at the U.S. Patent and Trademark Office, Sandoz and other filers, along with the court system, endured multiple waves of litigation on terminally disclaimed patents, spanning more than a full decade and costing Sandoz the equivalent of development costs for five or six new generic products. And when Sandoz continued to litigate, despite other generic filers entering into settlements, the originator company responded by initiating yet another litigation, pursuing Sandoz until Sandoz finally settled in 2022.

Had an approved generic product been able to launch in 2016, doing so would have saved the U.S. healthcare system approximately an additional 417 million USD.[90]

[86] Allergan, Inc. v. Sandoz Inc., No. 12-cv-00207 (E. D. Tex. Dec. 30, 2016), ECF 352.
[87] Allergan Sales, LLC v. Sandoz, Inc., 717 F. App'x 991, 994 (Fed. Cir. 2017).
[88] Amended Complaint at para. 32, Allergan Sales LLC v. Sandoz, Inc., No. 2:17-cv-10129 (D.N.J. April 6, 2018), ECF No. 66.
[89] Allergan Sales LLC v. Sandoz Inc., 935 F.3d 1370, 1371 (Fed. Cir. 2019).
[90] Calculated as follows: (WAC savings per standard unit by purchasing the generic product instead of the brand product) x (average standard unit volume of generic product sold per year in the first two calendar years of generic sales) x (years between 2016 district court decision and actual generic launch). Volume data obtained from IQVIA Analytics. WAC prices in standard units as of May 2024 obtained from Analysource.

Patent issues

Patent linkage

1.2. Patent linkage

Patent linkage describes a practice whereby the ability of a generic or biosimilar product to obtain a marketing authorisation or other administrative approvals or procedures required before market entry is linked to the status of a patent pertaining to the reference product. In some jurisdictions, patent linkage has been introduced in the system together with incentives to challenge patents. In other jurisdictions, patent linkage is considered unlawful since public regulatory and administrative processes and decisions should remain entirely independent from the status of any patent, given the rights afforded by a patent are private rights to be disputed under the current patent system between private entities. Certainly, the issue of whether a medicinal product infringes a patent, and so whether that medicinal product should be able to be sold, should not be a question to be determined by any public authority other than a court.

Existing patent linkage systems are being misused or abused as an evergreening strategy to trigger unnecessary litigation and unduly block legitimate generic and biosimilar products. Even in those regions where patent linkage is illegal, the artificial linkage of the patent status to these processes is readily exploited as a tactic designed to hinder market entry for generic or biosimilar products. In practice, this strategy is effective and is particularly problematic where the patent being relied upon is ultimately found to be invalid, as stressed in the trilateral study of the World Trade Organisation (WTO), the World Intellectual Property Organisation (WIPO) and the World Health Organisation (WHO) of 2020: "*[t]he regulatory agency may refuse to register generic products based on the existence of patents that should not have been granted in the first place*".[91]

1.2.1. Canada

Patent linkage in Canada, was established through the Patented Medicines (Notice of Compliance) Regulations (PMNOC regime)[92] in 1993. Automatic injunctions of up to 24 months are available to originator companies under the regime, with no upfront burden of proof.

Some examples of patent linkage in combination with patent thickets can be found in Invega® (paliperidone); Januvia® (sitagliptin); Opsynvi® (macitentan); and, Esbriet® (pirfenidone). These cases highlight one of the implications as a result of patent linkage, namely the delay generic and biosimilar market entry.

Invega® (paliperidone)

This is a patent linkage case in which the patent at issue was a use patent (often called a method of treatment). The originator company obtained an injunction that prevented making, and using the generic product over the broad scope of approved dosage regimen despite the fact that the patent at issue only covered a specific dosage regiment prescribed for only about 15% of patients.

Protection for the active ingredient and whole scope of indications has been extended by the injunctive relief granted. Making and importing the unprotected active ingredient has been prohibited by a use patent.[93]

Januvia® (sitagliptin)

[91] "Erroneously granted patents may lead to costly litigation and delay entry of generic versions, thus negatively impacting access to medicines. They can also become problematic with regard to patent linkage, for instance, when the grant of marketing approval for medicines is linked with patent status" 2020 WTO-WIPO-WHO Trilateral Study "Promoting Access to Medical Technologies and Innovation", p. 232.
[92] See https://laws-lois.justice.gc.ca/eng/regulations/sor-93-133/Fulltext.html.
[93] 2023 FCA 253; 2024 FCA 23; 2023 FCA 68.

In this case, a salt patent's validity was assessed not on whether the salt form was inventive but whether selecting the active ingredient of sitagliptin to make a salt form was inventive effectively permitting the originator company to rely on the invention story of the active ingredient rather than the salt.

The court dismissed Pharmascience's allegation that Canadian Patent No. 2,529,400 was invalid for obviousness and/or insufficiency and declared that the making, constructing, using or selling by Pharmascience of its generic sitagliptin phosphate tablets in strengths of 25 mg, 50 mg and 100 mg in accordance with the Abbreviated New Drug Submission bearing Submission No. 233922 would directly or indirectly infringe at least one of claims 4-7, 19, 20, 22, 24 or 26 of Canadian Patent No. 2,529,400.[94] This decision had the impact of delaying the market entry for generic versions of sitagliptin in Canada by two years, until the patent in question expired.

Opsynvi® (macitentan)

The patent at issue acknowledged that the compound was old and covered the combination of macitentan in combination with a PDE5-inhibitor. Apotex was prevented from selling a generic version of macitentan, even though the indications in the proposed product monograph did not include the combination.

The patent in question does not expire until August 28, 2027.[95]

Esbriet® (pirfenidone)

This case pertains to generic pirfenidone capsules. Two patents were in issue: one for dose escalation and one for treatment after this patient has exhibited a grade two abnormality in one or more biomarkers of liver function, following treatment with pirfenidone.[96] Sandoz was sued on seven different patents that were listed on the Health Canada Patent Register by the originator company but only two of these patents went to trial.

Sandoz succeeded in the litigation, but had to bear very significant litigation costs. However, due to the mandatory stay to approval contained in the patent linkage system, the mere fact of the litigation meant Sandoz was not able to launch the medicinal product until May 2021, despite receiving regulatory approval in October 2020.

[94] 2022 FC 417.
[95] Janssen Inc. v. Apotex Inc., 2022 FC 996, upheld Apotex Inc v Janssen Inc, 2023 FCA 220.
[96] Hoffmann-La Roche Limited v. Sandoz Canada Inc., 2021 FC 384.

1.2.2. European Union

In the European Union, patent linkage is considered "*unlawful*"[97] as potentially anti-competitive, since it can systematically delay generic or biosimilar market entry. It is considered in contrast with the European legislative framework since regulatory, pricing and reimbursement or tender authorities, while making their (public) decisions on the approval of medicinal products, have no competence or knowledge to evaluate whether a patent (a private right) is valid or relevant. This is a competence of courts. As the European Commission clarifies:

> "*[s]uspending the price approval procedure for any other reason than the ones indicated in the Transparency Directive is considered as a breach of the Directive*"[98] and "*[u]nder EU law, patent protection is not a criterion to be considered by the authorities when approving prices or granting reimbursement status*."[99] Therefore, "*Member States should disregard third party submissions raising patent, bioequivalence or safety issues*".[100]

However, in the European Union, the existence of a patent, even if irrelevant to the market entry of a generic or biosimilar product, enables originator companies to use the unlawful patent linkage to delay or block pricing and reimbursement or tender procedures for generic and biosimilar products. The existing forms of unlawful patent linkage in the European Union are in relation to:

- Marketing authorisations: An originator company may exploit or misuse procedures for the granting of a marketing authorisation for a generic or biosimilar company claiming that the application for a marketing authorisation represents an infringement of its relevant patent(s). A marketing authorisation application by a competitor results in litigation proceedings being issued by an originator company. This practice exists in Portugal.
- Pricing and reimbursement: In some Member States, the relevant agencies will refuse to approve the pricing and reimbursement of generics and biosimilars simply due to the existence of a patent. In addition, the act of seeking pricing or reimbursement approval can be considered an infringement of a patent allowing patentees to seek injunctions against those authorities to prevent them from carrying out pricing and reimbursement activities in relation to a generic or biosimilar product during a patent term.
- Procurement: An originator may exploit and/or misuse procedures for communication with competent authorities for procuring medicinal products in Member States to perturb generic and biosimilar companies from entering these markets.
- Prescription listing: In order to be available for prescription by healthcare practitioners in some Member States, a medicinal product must be listed in a prescription listing, or formulary. Patentees may assert that this listing is an act of patent infringement and, based upon the listing, seek judicial relief on the basis of granted patents.

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[97] European Commission's 2009 Pharmaceutical Sector Inquiry Report, p. 315: https://competition-policy.ec.europa.eu/system/files/2022-05/pharmaceutical_sector_inquiry_staff_working_paper_part1.pdf.
[98] See European Commission Sector Inquiry Report of 2009, p. 328.
[99] See European Commission Sector Inquiry Report of 2009, p. 330.
[100] See European Commission Sector Inquiry Report of 2009, p. 532.

Non-judicial authorities are not competent to evaluate patent infringement. Patent linkage by-passes judicial proceedings in that the authorities which are responsible for pricing and reimbursement, procurement, prescription listing etc., are not equipped to evaluate patent infringement or validity. In practice, the patentee informs the authority about a patent, in some cases even a questionable secondary patent, and the authority generally would act upon this information by blocking the steps of the generic and biosimilar companies necessary to prepare launch of their medicinal product. The launch is delayed for weeks, months or years, without any court decision or court proceedings where the arguments of the generic or biosimilar company are heard.

Ultimately, patent linkage activities hinder and delay access to the European market for generic and biosimilar products, to the ultimate detriment of patients and healthcare providers. Furthermore, patent linkage brings about a number of specific disadvantages. For example:

- Limited compensation for delay: If patent linkage is enshrined in legislation or national practices and the competent authority is acting in accordance with such legislation or practice, there is often limited, if any, compensation available to the manufacturer of the medicinal product who suffers delayed market access. The same is also true for the health services and patients deprived of competition and lower cost medicinal products. This is so, notwithstanding the European Commission's view that linkage is contrary to European law.
- Undermining of the Bolar provision: The purpose of the so-called "Bolar provision" is to allow generic and biosimilar companies to conduct the necessary studies and clinical trials required to obtain marketing authorisation and to undertake regulatory and administrative activities without the risk of patent infringement proceedings being brought against them, with the ultimate objective to allow generic and biosimilar medicinal products to be ready for launch immediately at expiry of intellectual property. Linkage of the regulatory approval processes to patent infringement directly undermines this provision and may result in generic and biosimilar companies undertaking those activities only upon patent expiry, thereby delaying access of those products to the market.
- Cost of patent-based litigation to generic companies: Patent linkage is conducive to a proliferation of patent-based litigation, which creates additional costs for generic companies seeking to enter the market. The 2009 Commission Report found that the estimated total cost of patent litigations in the European Union between 2000 and 2007 was in excess of 420 million EUR.[101] The general perception is that the situation has not improved since 2009.

There are many cases in the European Union in which patent linkage is identified. These cases relate, for instance, to Truvada® (emtricitabine and tenofovirdisoproxil fumarate); Xalatan® (latanoprost); Janumet® (sitagliptin and metformin hydrochloride); Xarelto® (rivaroxaban). These cases underline the significant impact on the healthcare budgets of the Member States, as well as to patient access to affordable treatment.

Truvada® (emtricitabine and tenofovir disoproxil)

Truvada®, a fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), is a critical medicinal product for treatment and prevention of human immunodeficiency virus (HIV). Also used as pre-exposure prophylaxis (PrEP), it can reduce HIV transmission by over 90% in sero-discordant couples. Its basic patent, EP 0 915 894, expired in July 2017 and claimed only tenofovir disoproxil, and not emtricitabine. Despite the fact that the patent did not qualify for a supplementary protection certificate, the originator company

[101] See https://competition-policy.ec.europa.eu/sectors/pharmaceuticals-health-services_en.

managed to convince some national patent offices to grant a supplementary protection certificate to extend patent protection for Truvada® in some Member States (e.g. France, Germany, Spain, Italy, Portugal, Ireland), while the supplementary protection certificate was not granted in other countries (e.g. the Netherlands, Greece).

In 2017 and 2018, national courts invalidated the illegitimate supplementary protection certificate in all countries and the supplementary protection certificate was ultimately declared illegitimate by the European Court of Justice[102] upon reference by the UK High Court, which in its final judgement stressed that "*SPC [supplementary protection certificate] Regulation is to enable the holder of the basic patent to obtain supplementary protection for what the patentee actually invented and not for what the patentee did not invent*."[103]

However, due to longer court procedures in Portugal and the patent linkage mechanism then in place in Portugal, 95.000 Portuguese patients had delayed access to generics HIV treatment and incurred additional costs for the Portuguese healthcare system of 109 million EUR (equivalent to 1.1% of total 2018 health budget).

Similar delays occurred in Italy, again due to the interaction between the patent linkage system in Italy that prevents generic companies from obtaining pricing and reimbursement while there is a patent right in force, and the slow court decision revoking the invalid SPC.[104] In the Netherlands, for example, where the generic product was not delayed since the illegitimate supplementary protection certificate had not been granted, and therefore enforced, the price of TDF/FTC had dropped from 344,28 EUR (Truvada®) for a 30-day supply to 47,95 EUR for the generic product.

Xalatan® (latanoprost) – Patent linkage and divisional game

Xalatan® is a critical medicinal product for eye glaucoma. The original patent (EP 1 225 168) was set to expire in September 2009. The originator company filed for, and obtained, a divisional patent (EP 0 364 417) followed by a supplementary protection certificate and a paediatric extension.

In Italy, the combination of the originator company's patent, supplementary protection certificate and unlawful patent linkage strategy had managed to extend the duration of its monopoly by seven months until May 2010. In Italy, in fact, the mere listing of a supplementary protection certificate on a public register prevents generic products from being included in the reimbursement list of the Italian Medicines Agency. The Italian competition authority found evidence that the sole purpose of this strategy was to delay the onset of generic companies in the Italian market. The Italian Council of State confirmed this decision on appeal in 2014. A fine of 13.4 million EUR for the originator company was confirmed by the Italian Supreme Court in January 2024.[105] In addition to delaying patient access to generic treatment, this evergreening strategy taking advantage of unlawful patent linkage cost the Italian Health service an additional 14 million EUR.[106]

[102] CJEU's judgment in C-121/17.

[103] Teva v Gilead ([2018] EWHC 2416 (Pat)), para. 10. In paras 23-35, Arnold J. also addressed Gilead's application to admit further evidence and have a further 2-3 day trial, stressing that it would be an "abuse of process" analogous to attempting to amend patent claims after trial, as it was "an attempt by Gilead to amend its case and adduce fresh evidence after trial and judgment, and thereby get a second bite at the cherry".

[104] See https://medicineslawandpolicy.org/2018/05/will-the-european-court-of-justice-put-a-stop-to-the-evergreening-of-truvada-patents/; https://www.medicinesforeurope.com/wp-content/uploads/2023/10/Updated-Medicines-for-Europe-Bolar-Patent-Linkage-Paper-20-Oct-2023-1.pdf.

[105] Decision no. 9/2024 published on 2 January 2024.

[106] See https://www.medicinesforeurope.com/wp-content/uploads/2023/10/Updated-Medicines-for-Europe-Bolar-Patent-Linkage-Paper-20-Oct-2023-1.pdf.

Janumet® (sitagliptin and metformin hydrochloride)

For the treatment of type 2 diabetes, the originator company obtained two supplementary protection certificates for two medicinal products: Januvia® (sitagliptin), whose supplementary protection certificate expired on September 23, 2022, and Janumet® (combination of sitagliptin and metformin, an older active ingredient with expired patent), whose supplementary protection certificate expired on April 7, 2023.

In light of the recent European Court of Justice and national jurisprudence on analogous supplementary protection certificate cases (see the Truvada® case above) the supplementary protection certificate on the combination of sitagliptin and metformin (Janumet®) had already been declared illegitimate and invalidated in Germany by the German Federal Patent Court on June 23, 2021.[107] However, in Italy, due to longer court procedures for formally invalidating the supplementary protection certificate, the unlawful Italian patent linkage system blocked the reimbursement of the generic version of sitagliptin/metformin from September 23, 2022 until April 7, 2023 (i.e. the expiry date of the illegitimate supplementary protection certificate). The distortion of competition created by the Italian patent linkage system delayed patient access to the generic version of Janumet® by approximately six months, costing the Italian healthcare system at least 9.8 million EUR.[108]

Xarelto® (rivaroxaban)

The originator company sued the *Informationsstelle für Arzneispezialitäten IFA GmbH* (IFA - the information and registration organisation responsible for the German Pharmaceutical Central Numbering system) and requested a preliminary injunction not to list generic products containing rivaroxaban in the so-called *Lauer-Taxe*. The patent involved expires in January 2026, but has been being declared invalid by the UK and French courts.

Since the German Federal Patent Court had considered the patent to be valid in a preliminary opinion, the Munich Regional Court also issued preliminary injunction orders against the generic companies that were applying for IFA listing. Therefore, while the case continues before German courts, the supplementary protection certificate of Xarelto® expired in April 2024, and generic companies are still prevented from listing on the IFA list due to patent linkage. The IFA as a neutral administration should not be involved in a patent infringement case for or against generic products. Furthermore, it lacks information and capacity to properly defend non-infringement of generic products. The parties defending generic products should be the generic companies requesting to list their products. The effect of this action is patent linkage and automatically delays the launch of generic products, without properly hearing the generic companies´ arguments. Any appeal by the generic companies will take months. The question of patent infringement should be dealt with only by the interested parties, e.g. the patentee and the generic marketing authorisation holder. The patentee should not be allowed to sue the IFA for listing medicinal products. The IFA should remain what it is: a neutral administrative body listing or delisting medicinal products based on a formal examination and not evaluating patent infringement.

[107] Case nos. 3 Ni 2/20, 3 Ni 24/20, 3 Ni 3/21.

[108] See https://www.taylorwessing.com/en/insights-and-events/insights/2022/03/german-federal-patent-court---janumet-spc. The annual expenditure to be borne by the Italian NHS for the MSD Janumet® was approximately € 38 million (estimate based on IQVIA data, MAT Feb 2022) and generic medicines should have had a reduced price of at least 47,5% (pursuant to the Health Ministerial Decree of 4 April 2013). This would have resulted in a minimum monthly saving of approximately € 1.5 million (further increased by the regional tendering mechanism).

In this case, the impact of patent linkage being enforced in such a legally uncertain situation has a huge impact, not only on access to generic treatment, but also on healthcare budgets, considering that sales of Xarelto® amounted to around 4 billion EUR in 2023.[109]

In the table below, there are some examples of delayed market entry due to different forms of "patent linkage" as reported by Medicines for Europe and showing the concrete, huge negative impact the linkage between generics regulatory procedures and the status of patents/ supplementary protection certificates has on patient access to treatment and on savings for healthcare systems:

Molecule	Treatment	Country	Originator approval	SPC Expiry	Generic Entry	Delay	Cost of Delay: Lost Savings in EUR
Oxycodone/ Naloxone	severe pain	Germany		29/3/2017	15/11/2017	231 days	**51,6 Mln**
Ezetimibe/ simvastatin	high cholesterol	Italy	18/11/2004	16/10/2017	9/3/2018	144 days	**15,4 Mln**
Ezetimibe/ simvastatin	high cholesterol	Germany	18/11/2004	17/4/2018	15/5/2018	28 days	**11,3 Mln**
Lenalidomide	multiple myeloma, cancer	Hungary	14/06/2007	19/6/2022	1/6/2023	347 days	**1.9 Mln**
Pirfenidone	idiopathic pulmonary fibrosis	Germany	27/02/2011	27/2/2021	15/11/2022	626 days	**32,1 Mln**
Tapentadol	severe pain	Germany	19/08/2010	07/12/2020	15/1/2023	917 days	**184,6 Mln**
Dasatinib	chronic myeloid leukemia	Poland	20/11/2006	22/5/2022	01/01/2023	224 days	**4,5 Mln**
Total:						**2,517 days**	**301,4 Mln**

A more detailed analysis of patent linkage in the European Union with additional data and examples is available on Medicines for Europe's website[110].

[109] See: https://www.statista.com/statistics/263787/revenues-of-bayers-top-pharmaceutical-products/.
[110] See https://www.medicinesforeurope.com/wp-content/uploads/2023/10/Updated-Medicines-for-Europe-Bolar-Patent-Linkage-Paper-20-Oct-2023-1.pdf.

1.2.3. India

India has no patent linkage system. Generic and biosimilar companies can seek marketing approval for medicinal products even if the patent for the reference product is still in force. However, the approved generic or biosimilar product should not be launched if the patent for the reference product remains in force. India's patent and marketing approval processes are overseen by separate authorities: the Indian Patent Office grants patents, while the Central Drugs Standard Control Organization (CDSCO) provides marketing approval for medicinal products in accordance with the Drug and Cosmetic Act of 1940.

Indeed, in India, the idea of patent linkage has been comprehensively denied as seen in the litigation regarding Nexavar® (sorafenib). This case was the first comprehensive examination of patent linkage within the Indian legal framework, and it definitively affirmed its absence. Its implications extend to public health considerations, as the originator company's advocacy for patent linkage could potentially have impeded the timely entry of generic products into the market, thereby affecting medicinal accessibility.

Nexavar® (sorafenib)

In March 2008, the originator company obtained a product patent (IN215758) from India's Patent Office for sorafenib, a pharmaceutical compound commonly utilized in the treatment of advanced renal cancer. In July 2008, the originator company was made aware of an application submitted by Cipla, a pharmaceutical entity, seeking approval to market a generic version of sorafenib. The originator company wrote a letter to the Drug Controller General of India *inter alia* requesting that marketing approval not be granted to Cipla for its medicinal product "Soranib". Following this objection, the originator company initiated a writ petition in the Delhi High Court, restraining the Drug Controller General of India from granting a licence to Cipla to manufacture and market, to imitate/substitute sorafenib tosylate protected under subject patent number 215758. The Drug Controller General of India contested the originator's position, asserting the autonomous operation of the Drugs and Cosmetics Act and the Patents Act, which precluded the denial of Cipla's approval on grounds of patent infringement under the Drugs and Cosmetics Act.

In August 2009, the Delhi High Court made the following findings:

- The Delhi High Court found no basis in the argument of "patent linkage", noting that the Drugs and Cosmetics Act and the Patents Act serve distinct purposes with disparate objectives. They concluded that there is no inherent connection between the two statutes.
- The court rejected the notion that the grant of a patent under the Patents Act automatically prohibits non-patent holders from seeking marketing approval under Section 2 of the Drugs and Cosmetics Act. They emphasised that the Parliament did not intend such a restrictive interpretation.
- The court criticized patent linkage for effectively transforming private patent rights, dependent on the owner's enforcement decisions, into public rights governed by statutory authorities. This shift, they argued, would undermine the "Bolar/Early Working" exception and restrict the entry of generic medicinal products into the market. [111]

These findings underscore the court's view on the intersection and implications of patent and drug regulatory laws in India.

[111] Bayer Corporation and Others v. Cipla of India (UCI) and Others.

Subsequently, the originator company pursued an appeal before the division bench of High Court of Delhi (appeal court). In February 2010, the appeal Court upheld the Delhi High Court ruling, elucidating that there is no patent linkage in India. Furthermore, the appeal court emphasised that the mere inclusion of a "patent status" section in a marketing approval application did not establish patent linkage. The court underscored the international trend of scepticism towards patent linkage, citing concerns regarding public health. Consequently, the originator company's appeal was dismissed.

In March 2010, the originator company subsequently appealed to the Indian Supreme Court; however, the appeal was dismissed in December 2010. The Supreme Court observed that the Drug Controller General of India had already granted marketing approval to Cipla, while the originator company's infringement suit remained pending before the Delhi High Court, where the originator company sought an injunction.

1.2.4. Japan

In Japan, patent linkage is not governed by law but by a notification on behalf of two directors of the Ministry of Health, Labour and Welfare for the purpose of ensuring continuous supply of generic products. The notification was originally issued in 1994, which was later revised in 2009 to inable the approval of generic products in accordance with a skinny label. When the Evaluation and Licensing Division finds a patent, which might pose a risk of patent infringement due to the approval of a generic product, the approval of the medicinal product is suspended until the patent expires, or until an invalidation decision is made.

The applicant for the generic product has no right to file an objection to the suspension of the approval of the generic product with the Ministry of Health, Labour and Welfare. There is no legal basis. Sometimes, an uncontrollable deadlock situation occurs due to patent linkage since the subject of the patent linkage includes not only the second medical use patent but also a wide-variety of patents directed to a subpopulation of patient groups.

Patent linkage in Japan can be identified in the context of Halaven® (eribulin mesylate). This case clearly demonstrates the significant impact on the healthcare budgets as a result of patent linkage.

Halaven® (eribulin mesylate)

Due to patent linkage, it is estimated that the launching of the generic product will have to wait until June 2034, since the generic version of the eribulin mesylate injection will only be approved on February 15, 2034, after the expiration of the originator company's "subpopulation patent" JP6466339 and JP6678783 on December 4, 2033, and thereafter it will be listed in the prescription medicinal product price listing in June 2034. Since the

originator company's reference product was launched on July 19, 2011, the originator company would be enjoying a monopoly over 23 years.[112]

According to the financial statement of the originator company, annual sales of Halaven® in Japan were approximately 8.3 billion JPY in 2021. A generic version of Halaven® could have been launched in June 2021 if JP6466339B and JP6678783B had not been subject to patent linkage. In that case, on the assumption that the generic product takes 80% of market volume share, 3.32 billion JPY of national drug expenditure is the estimated saving in a year. Unexpectedly, a generic version of Halaven® was approved for a generic company in August 2024, but the reason of such sudden approval has not been announced.

1.2.5. Middle East and North Africa

There are three types of patent linkage in the Middle East and North Africa, which can be identified in Morocco, the Kingdom of Saudi Arabia and Bahrain and the United Arab Emirates.

- Morocco: Patent linkage with a legal basis and without a framework

Article 16 of Law No. 17-04 on the Code of the Medicine and Pharmacy (November 22, 2006) in Morocco prevents the commercialisation of generic products before the expiry date of the patent that protects the reference product. This article does not define the type of patent that protects the reference product. It is unclear whether it refers to the product patent only or whether other type of patents (formulation, use, etc.) are included. Also, there is no framework that regulates the registration and commercialisation of non-infringing generic products.

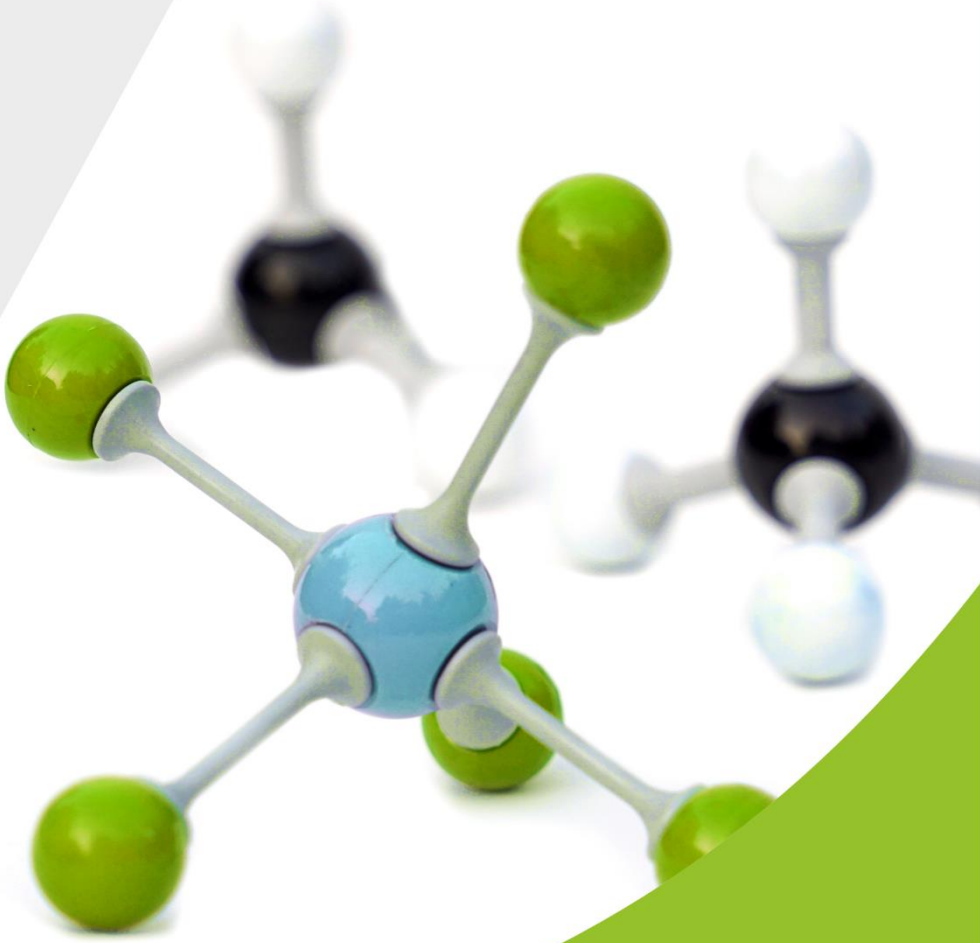
- Kingdom of Saudi Arabia: Patent linkage with a legal basis and framework

The Saudi Drug and Food Authority (SFDA) in cooperation with the Saudi Authority for Intellectual Property published, in November 2022, a new regulation that provides a framework for the registration of generic products while there is a valid patent in Kingdom of Saudi Arabia, this regulation came into force on January 1, 2023. The generic companies will either submit a Freedom to Operate letter issued by an intellectual property agent licensed by the Saudi Authority for Intellectual Property that proves that the generic product does not infringe the patent filed in the innovated product file at the SFDA, or the generic companies will submit the file six month before the expiry date of that patent.

- Bahrain and United Arab Emirates: Patent linkage without a legal basis and a framework

In Bahrain, there are no articles, either in the patent law nor in the medicine and pharmaceutical product registration regulations, that link registration of generic products with the patent status. However, the health authority may suspend/reject the registration file if there is a granted patent in Bahrain. In the United Arab Emirates, the Ministry of Health and Prevention links the file submission of generic products with the patent status in the country of origin without any legal basis. The Ministry of Health and Prevention does not publish the chosen country of origin or the patent status in that country and leaves the choice of the country of origin to the originator company.

[112] Nipro vs Eisai, 2022-Ne-10093 (IP high court) and its original verdict 2021-wa-13905 (Tokyo district court).



Patent issues

Second medical use patents and skinny labelling

1.3. Second medical use patents and skinny labelling

A reference product may be covered by multiple patents. Among these patents, there are indication (or medical use) patents. Therefore, when a medicinal product is already approved for one medical use, second or subsequent medical uses may still be patented at any point in time after the initial approval of the reference product. As a consequence, a certain medicinal product may open to competition for certain uses, but not for others. When this is the case, skinny labelling allows generic and biosimilar products to be approved for non-patented indications, facilitating timely entry of generic and biosimilar products. A "skinny label" is when generic and biosimilar companies carve out from their labels the patented indications in order to be able to enter the market for the indications whose patents have already expired. Without skinny labelling, market entry of generic and biosimilar companies would be delayed by multiple years due to the subsequent indications often approved and patented for the reference product. Indeed, skinny labels prevent originator companies from artificially delaying competition by obtaining patents covering subsequent indications at different points in time.

While indication carve-outs are permitted by regulatory authorities, generic and biosimilar products may be delayed or subject to huge legal uncertainty and unnecessary litigation due to allegations of patent infringement by originator companies.

1.3.1. Canada

In Canada, a generic company typically cannot be held liable for directly infringing a use patent. This is because the manufacturer does not itself use the medicinal product. It is the patient that uses the medicinal product as prescribed by the physician and dispensed by the pharmacist.

However, generic companies have been held to be liable for indirect infringement of use patents. The typical basis for such infringement is via the generic companies' Product Monograph. The Product Monograph is the document required by Health Canada to be made available to physicians, pharmacists and patients in respect of the medicinal product in question. While the test for indirect patent infringement is inconsistently applied in Canada, where the Product Monograph is said to "instruct" the infringing use, the generic company can potentially be held liable for having induced infringement of a use patent.

One means by which generic companies have historically attempted to avoid such liability is via a "skinny label", in which instructions as to the infringing use are "carved out" of the Product Monograph. To find infringement in such circumstances would, in the words of the Federal Court of Appeal, result in "*an artificial extension of the monopoly*" afforded by the patent: "*The patent holder would, therefore, effectively control not just the new uses for the old compound, but the compound itself, even though the compound itself is not protected by the patent in the first place*".[113]

[113] AB Hassle v. Canada (Minister of Health and Welfare), 2002 FCA 421 at para. 57 and Aventis Pharma Inc. v. Pharmascience Inc., 2006 FCA 229 at para. 58.

However, the recent decisions of the Federal Court of Canada and Federal Court of Appeal appear to have narrowed the scope of the Canadian "skinny label" doctrine. Proof can be found in the context of Opsumit® (macitentan).[114]

Opsumit® (macitentan)

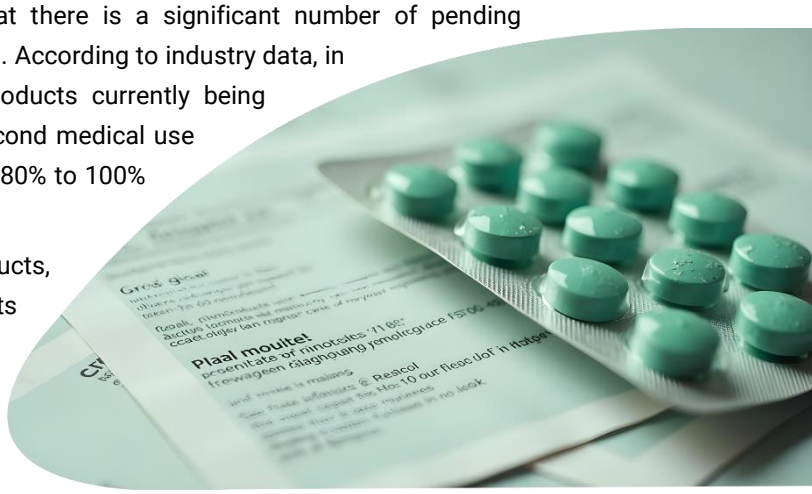
The patent in question claimed the use of macitentan in combination with a PDE5-inhibitor for the treatment of pulmonary arterial hypertension. Apotex obtained a "skinny label" Product Monograph that excluded an indication for the claimed combination treatment. Apotex was nonetheless held liable as an indirect infringer, on the basis that (a) the few physicians permitted to prescribe the medicinal product in question would be aware of a landmark clinical study known as "Seraphin", which showed that both a non-infringing and infringing use of the medicinal product was safe and effective; (b) a significant portion of the information in the Apotex Product Monograph was data from the Seraphin study; and (c) physicians would review and rely on Apotex's Product Monograph.

As one commentator put it, the "*implication is that it is simply not possible for Apotex to sell macitentan for the unpatented use*".[115] This is because the only permissible "skinny label" would have to "carve out" so much information from the Product Monograph, including in respect of non-infringing uses, that the Product Monograph would not meet Health Canada's requirements for approval.

1.3.2. European Union

The existence of second medical use patents produces a series of effects of legal, regulatory and market access relevance. Generic and biosimilar companies can carve out patented indications from the summary of product characteristics and the product information leaflet to avoid allegations of patent infringement (in accordance with Article 11 of Directive 2001/83 and Article 3.3 (b) of Regulation 726/2004). However, since the prescription or dispensation of a generic product for a patented/carved out indication depends on the activities of doctors or pharmacists, severe litigation has developed in the EU on this matter and jurisprudence has been attempting to clarify in what cases generic companies may be exempted from direct or indirect patent infringement.[116]

This may be even more problematic considering that there is a significant number of pending applications and patents claiming second medical uses. According to industry data, in the European Union, up to 60% of the medicinal products currently being developed by generic companies have at least one second medical use patents. For biosimilar products, this figure goes up to 80% to 100% of the cases.



For all medicinal products, but especially oncology products, there is a clear trend to file a dense net of use patents comprising not only new illnesses but also combinations with chemotherapy, patient subpopulations, patient monitoring, use of predictive biomarkers, dosage regimens, etc. The claims often

[114] Janssen Inc. v. Apotex Inc., 2022 FC 996, aff'd 2023 FCA 220.
[115] Siebrasse, "Inducement in the Pharma Context is an Inherently Hard Problem", Nov. 15, 2023, Sufficient Description.
[116] For instance, see: Warner-Lambert Company LLC (Appellant) v Generics (UK) Ltd t/a Mylan and another (Respondents), [2018] UKSC 56; or Warner-Lambert Company, LLC vs. Aliud Pharma GmbH, Regional Court of Hamburg; or Novartis v Sun Pharmaceutical Industries, District Court of The Hague, ECLI:NL RBDHA:2015:14337. Several other cases have taken place throughout Europe.

mirror the labelling in the summary of product characteristics, which undergoes variations over the years. Despite the fact that most patent applications will not be granted or revoked after grant, this leads to long periods of uncertainty for the biosimilar companies and to significant costs for pre-grant and post-grant legal actions.[117]

As an additional complication, when the use patent covers a safety profile of medicinal products, the authorities insist on keeping this information on generic and biosimilar products in the summary of the product characteristics/product information leaflet due to public health reasons. This requirement creates a basis for litigation by the originator companies, which tend to sue not only the generic or biosimilar companies, but also health authorities in some circumstances. This is clearly demonstrated in the context of Lyrica® (pregabalin).

Pregabalin (Lyrica®)

The originator company markets a product called Lyrica® (pregabalin) that is approved for three separate indications: epilepsy, generalised anxiety disorder, and neuropathic pain. Marketing authorisations for generic versions of pregabalin were obtained in the Netherlands after expiry of regulatory data protection and generic companies had carved out the patented indications. The Dutch Medicines Evaluation Board then, for public health reasons, published on their website the full label summary of product characteristics and product information leaflet for the generic pregabalin.

However, the European Court of Justice stated that the Dutch Medicines Evaluation Board had to replace the full label summary of product characteristics and product information leaflet for generic pregabalin on its website with the carved out versions provided by the generics, as otherwise the Dutch Medicines Evaluation Board would not actually directly and indirectly infringe the medical use patents, but would be unlawful as incompatible with the Dutch Medicines Evaluation Board's duty of care vis-à-vis the originator company.[118]

This case shows the huge legal uncertainties that generic and biosimilar companies need to face when launching products with carve-outs, which is even aggravated by the fact that launches take place in multiple European countries, which all have different approaches to second medical use patents. Therefore, litigation is a constant risk.

All these legal uncertainties created by the intricate network of second medical use patents have a very direct impact on generic and biosimilar companies. The costs of litigation for companies in cases of second medical use patents reach 10 million EUR and are estimated to be increasing, according to industry data. Such costs have a tangible impact for companies and risk being reflected in the prices and availabilities of generic products in certain countries.

[117] According to European Patent Office statistics, in 2020, 68.9% of the opposed patents have been revoked or amended: https://oxonip.com/sites/default/files/publications/EPO_opposition_statistics_a%20five-year_review.pdf.
[118] Case C-423/17, referred to the European Court of Justice for a preliminary ruling by the Regional Court of Appeal, The Hague, Netherlands.

1.3.3. United States

Since the enactment of the Hatch-Waxman Act in 1984, generic companies have brought numerous generic products to the market via the "skinny labelling" (or "section viii" statement) mechanism that carves out reference product sponsors' patented methods of use from their approved labelling of the Food and Drug Administration. This carve-out process is expressly provided for in Hatch-Waxman. The rationale for carving out patented indications is straightforward: competition from generic companies is facilitated on unpatented uses of brand name medicinal products and patients are able to have timely access to more affordable medicine.

Despite this well-established practice, the Federal Circuit issued two recent decisions that create legal uncertainty and may limit generic companies' ability to launch early through skinny labelling in the context of Coreg® (carvedilol) and Vascepa® (icosapent ethyl).[119]

Coreg® (Carvedilol)

An originator company markets Coreg® (carvedilol), which was approved for three indications: hypertension, congestive heart failure, and the reduction of cardiovascular mortality after left ventricular dysfunction following a myocardial infarction (post-MI LVD).[120] The originator company had obtained a reissued patent directed to "decreasing mortality caused by congestive heart failure", which was published and listed in the Orange Book in 2008.[121] Teva Pharms. USA, Inc. (Teva) had obtained approval for a generic carvedilol product in 2007, and for a period of over three years, marketed the generic carvedilol with a "partial label" with only the hypertension and post-MI LVD indications.[122] During this time, Teva's press releases and marketing materials referred to its medicinal product as "AB-rated" to and a "generic version" of the originator company's Coreg®.[123] Thereafter and through June 7, 2015, Teva marketed its generic carvedilol with a "full label" of all three indications.[124]

The Federal Circuit, in an initial 2-1 decision issued on October 2, 2020[125], concluded that there was substantial evidence of patent infringement despite the fact that Teva's label contained, for three years, the very type of carve-out that is contemplated in the Hatch-Waxman Act. In February 2021, the Federal Circuit agreed to rehear the Teva case, in part, because of the ramifications that the decision would have on the generics industry. Next, the Federal Circuit vacated its October 2, 2020, judgment and withdrew the accompanying opinions. However, despite the rehearing, on August 5, 2021, the Federal Circuit again issued a 2-1 decision that arrived at

[119] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc. concerning GlaxoSmithKline LLC's (GSK) Coreg® (carvedilol)) and Amarin Pharma, Inc. v. Hikma Pharmaceuticals USA, Inc. (concerning Amarin Pharma, Inc.'s Vascepa® (icosapent ethyl)).
[120] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320, 1323 (Fed. Cir. 2021).
[121] Id. at 1324.
[122] Id. at 1325.
[123] Id. at 1324.
[124] Id. at 1325.
[125] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 976 F.3d 1347 (Fed. Cir. 2020).

substantially the same result.[126] The Federal Circuit again concluded that Teva's partial label did not effectively carve out the patented indication and, taken together with press releases and marketing materials that referred to Teva's product as "AB-rated" to—and a "generic version" of — Coreg®, induced infringement of the RE '000 patent. The case was appealed to the U.S. Supreme Court, which denied certiorari on May 15, 2023.[127]

This result — twice decided by the Federal Circuit (and now denied certiorari by the U.S. Supreme Court) — calls into question the statutorily permitted "skinny labelling" mechanism for avoiding a determination of induced infringement. As Federal Circuit Chief Judge Prost stated in her August 2021 dissent, this case does not represent "*a disagreement among reasonable minds about the individual facts [of the case],"* instead *"this case signals that our law on this issue has gone awry."*[128]

Vascepa® (icosapent Ethyl)

The originator company markets Vascepa® (icosapent ethyl), which was approved for two indications: the treatment of severe hypertriglyceridemia, and the treatment to reduce cardiovascular risk.[129] The severe hypertriglyceridemia indication was approved first.[130] At that time the originator company's original label included an express "limitation of use", stating that the effect of Vascepa® had not yet been determined on cardiovascular risks.[131] Subsequently, however, the Food and Drug Administration approved the cardiovascular risk indication, and the originator company removed the limitation of use from its label, adding the cardiovascular risk indication to the label and listing two patents directed to the cardiovascular risk indication in the Orange Book.[132] Hikma Pharmaceuticals USA, Inc. (Hikma) sought approval for a label that carved out the cardiovascular risk indication, but it did not include the limitation of use that was in the originator company's original label.[133] After Food and Drug Administration approved Hikma's generic icosapent ethyl product, Hikma issued a series of press releases and marketing materials referring to its medicinal product as a "generic version" of and "AB-rated" to Vascepa®.[134]

The originator company sued Hikma for infringement of claims directed to the cardiovascular risk indication. The district court granted Hikma's motion to dismiss the originator company's complaint, finding that Hikma's label did not plausibly teach cardiovascular risk reduction[135], and that Hikma's public statements could only be relevant to Hikma's intent to induce, and are not separate inducing acts.[136] On appeal, the Federal Circuit reversed.[137] Despite agreeing with the district court that Hikma's label alone does not induce infringement[138], the Federal Circuit emphasised that the originator company's theory was based on additional acts, including public statements by Hikma.[139] Relying heavily on the early stage of this case and the requirement that all the

[126] GlaxoSmithKline LLC v. Teva Pharms. USA, Inc., 7 F.4th 1320 (Fed. Cir. 2021).
[127] Teva Pharmaceuticals USA, Inc. v. GlaxoSmithKline LLC, 143 S. Ct. 2483 (2023).
[128] Id. at 1343.
[129] Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., 104 F.4th 1370, 1372 (Fed. Cir. 2024).
[130] Id.
[131] Id.
[132] Id.
[133] Id. at 1373.
[134] Id.
[135] Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., 578 F. Supp. 3d 642, 646 (D. Del. 2022), rev'd, 104 F.4th 1370 (Fed. Cir. 2024).
[136] Id. at 647.
[137] Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., 104 F.4th 1370 (Fed. Cir. 2024).
[138] Amarin Pharma, Inc. v. Hikma Pharms. USA Inc., 104 F.4th 1370, 1379 (Fed. Cir. 2024).
[139] Id.

allegations of the complaint are taken as true at that early stage, the Federal Circuit allowed the case to proceed.[140]

This decision by the Federal Circuit may make it harder for generic companies to avoid the expense of litigating even weak inducement claims. And cumulatively these cases provide that "skinny labelling" alone will not avoid all claims of infringement, particularly relating to post-launch claims directed to sales activity conducted by the generic company.

[140] Id.

Patent issues

Preliminary injunctions

1.4. Preliminary injunctions

A preliminary injunction is an interlocutory order issued by a judge early in a legal proceeding to stop the defendant from continuing its allegedly harmful behaviour. Requests for preliminary injunctions are widely used by originator companies to prevent generics and biosimilar companies from entering the market even without a proper assessment of the actual validity of the patents, contributing to facilitating evergreening strategies. Such strategies become even more sophisticated when patent thickets are enforced to delay the market entry of generic or biosimilar companies, as each of the patents creating the patent thicket can be used to obtain a preliminary injunction and block market entry of generic and biosimilar products.

1.4.1. Argentina

In Argentina, several examples of undue delay of patient access to generic products relating to preliminary injunctions can be identified. This is the case, for example, in the context of Zyprexa® (olanzapine polymorph); Taxotere® (docetaxel); and Videx® (didanosine).

Zyprexa® (olanzapine)

Based on a secondary patent covering the polymorphic form II of olanzapine, in 1999 and 2001, the originator company obtained precautionary measures that excluded eight generic companies from the market. In some cases, the defendants reached an agreement with the originator company. However, a judgment declaring the invalidity of the patent was issued only on March 16, 2016, leaving the generic companies out of the market basically until the expiration of the (invalid) patent on March 22, 2016.

In two other cases relating to the Sandoz and Ivax olanzapine products, the judges rejected the originator company's lawsuit years after the lawsuits were initiated because requesting and obtaining marketing authorisation did not infringe the patent[141] due to the Bolar exception. Finally, the generic competing laboratory (Beta) succeeded in having the originator company's patent declared invalid due to not meeting the novelty requirement.[142] Still, Beta was out of the market for sixteen years because a preliminary injunction had been granted against it.

These preliminary injunctions allowed the originator company to enjoy undue market exclusivity for more than ten years (from 1999 to 2010), with an estimated negative impact on the budgets of consumers and funders of at least 37.5 million USD.

Taxotere® (docetaxel)

In 2003, an originator company obtained preliminary injunctions against several generic companies, managing to remove them from the market for months, based on a secondary patent for docetaxel, which only protected a process to obtain docetaxel trihydrate, being the docetaxel in the public domain.

[141] Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala II, 29/11/2012, "Eli Lilly and Company y otro c/ Ivax Argentina S.A. s/ Cese de Uso de Patentes" (n° /2002); and Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala II, 8/02/2013, "Eli Lilly and Company y otro c/ Sandoz S.A. s/ Cese de Uso de Patentes" (n° 12199/2002).
[142] Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala I, 15/03/2016, "Laborartorios Beta S.A. c/ Eli Lilly and Company s/ Nulidad de Patente" (n° 4620/01) y"Eli Lilly and Company c/ Laboratorios Beta S.A. s/ Cese de Uso de Patentes" (n° 8760/01).

Two generic competitors sued the originator company for damages, and final judgments were granted, awarding damages of around 2,000,000 USD in 2010 and 2013.[143] However, these judgments did not fully compensate the generic companies' losses and did not recover the position in the market that they had achieved before the preliminary injunctions. It also did not compensate the Argentinian healthcare system for the savings they lost due to the delayed launches, estimated at 35,400,000 USD between 2003 and 2018.

Videx® (didanosine)

In 2007, the originator company requested and obtained a preliminary injunction ordering the Ministry of Health of Argentina to suspend acquisitions of didanosine from the generic company Laboratorios Richmond S.A. As. The originator company requested the preliminary injunction based on a secondary patent for didanosine, which protected specific enteric-coated pharmaceutical beads of didanosine. Didanosine, the active ingredient was in the public domain.

Due to the preliminary injunction, a public tender in which Richmond had been the sole bidder to supply didanosine for 1800 patients was declared void. After its initial success, the Court of Appeal revoked the preliminary injunction, and the originator company finally withdrew the lawsuit.[144]

1.4.2. Canada

In Canada, apart from proceedings initiated under the Patented Medicines (Notice of Compliance) Regulations, which provide for an automatic injunction for up to 24 months in respect of patents listed on the Canadian patent register, preliminary injunctions in Canadian patent infringement cases are extremely rare. Invariably, the plaintiff is unable to establish the three required elements for a preliminary injunction, namely, a serious question to be tried, irreparable harm if no injunction is granted and balance of convenience favouring the grant of the injunction. In most cases, the plaintiff is unable to establish that it would suffer irreparable harm if no preliminary injunction were granted pending trial of the patent infringement suit.

In view of the foregoing, there are very few instances in Canada today where preliminary injunctions are sought in respect of patent infringement suits. That is not to say that, in an unusual set of circumstances, such as an infant developing market, unique market circumstances, and the like, it would not be possible to obtain a preliminary injunction. Much will depend upon the specific fact circumstances of the particular case.

[143] Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala I, 30/09/2010, "Laboratorios Richmond S.A. c/ Aventis Pharma S.A. s/ Daños y Perjuicios" (n° 15169/04); and Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala I, 10/09/2013, "Microsules de Argentina S.A. de S.C.I.I.A c/ Aventis Pharma S.A. s/ Daños y Perjuicios" (n° 5107/05).

[144] Juzgado Nacional de Primera Instancia en lo Civil y Comercial Federal Nº 9 Secretaría Nº 18, 1/4/2015, "Bristol Myers Squibb Company c/ Laboratorios Richmond S.A.C.I.F. s/ Cese de Uso de Patentes. Daños y Perjuicios" (n° 2656/2007).

1.4.3. European Union

Due to the fragmentation of the patent system in the European Union (27 different jurisdictions of the 27 Member States), the use of preliminary injunctions in conjunction with other patent strategies is particularly detrimental to timely access to the market for generic and biosimilar products. This is particularly the case for those jurisdictions where a preliminary injunction request is made to those courts that automatically grant preliminary injunctions, with no assessment (not even *prima facie*) of the validity of the patent which is unfortunately common in countries with courts which are less experienced in patent litigation.

The preliminary injunction proceedings (P.I.) initiated by the originator company in various countries on the basis of their patents in the context of Gilenya® (fingolimod) (as described in Section 1.1.1) are a good example of how this tool in combination with the divisional game is used to get protection to block generic companies from entering the market.

Gilenya® (fingolimod)

In the case of Gilenya® (fingolimod), there has been a lot of litigation on the basis of the indication patent EP 894 in several Member States. The impact of preliminary injunctions on the market entry of generic versions of fingolimod after preliminary injunction proceedings, in particular, is significant, as illustrated in the non-exhaustive below table.

Member State	Generic versions approved	Generic versions launched
Spain	32	9 – at least 3 temporarily blocked by P.I.[145]
Italy	19	0 – at least 1 blocked by P.I.
Germany	53	14 – all temporarily blocked by P.I.[146]

A further example of an effective immediate injunction is in the Czech Republic in the context of Tecfidera® (dimethylfumarate).

[145] In Spain, the preliminary injunctions were initially granted *inaudita altera parte* in March 2022, and lifted only in January 2023 for lack of inventive steps, delaying generics by 10 months.
[146] In Germany, the preliminary injunction was granted in January 2023 against all generics and then lifted in July 2023, leading to several months of unnecessary generic launch delay.

Tecfidera® (dimethylfumarate)

In the case of Tecfidera® (dimethylfumarate), the Czech customs acted upon a request from the originator company and seized generic dimethyl fumarate which was stored in warehouses in the Czech Republic. The effect of this is that the generic product cannot be sold, moved to another country or even destroyed before a court decision is taken on infringement/revocation of the patent, proceedings which take several years. This is equivalent to an *ex parte* preliminary injunction, without any court decision, and due to the shelf life of the product, the generic product becomes unusable.

1.4.4. India

The concept of "preliminary measures of protection" stands as a fundamental principle shared across all legal systems. These measures serve as temporary remedies designed to safeguard the rights of parties involved until a final judgment is rendered by the court. In patent infringement actions, the determination of rights typically occurs after a trial, during which evidence is presented by both the plaintiff and the defendant. Recognizing that trials can be time-consuming, the law also allows for the grant of interim relief in specific cases, provided certain conditions are met.

In India, a court may grant a preliminary injunction against the defendant if the following criteria are satisfied: (i) there is a *prima facie* case; (ii) irreparable harm is demonstrated; (iii) the patent is deemed valid and infringed; and (iv) the balance of convenience favours the injunction. *Ex parte* injunctions, where no notice is served on the defendants, may be granted if it appears that the purpose of the injunction would be defeated by a delay in notifying the defendants.

Recent examples of Revolade® (eltrombopag olamine) and Trajenta® (linagliptin) illustrate instances where courts have granted preliminary injunctions against generic companies. These examples clearly demonstrate the significant impact of preliminary injunctions on the market entry of generic and biosimilar companies.

Revolade® (eltrombopag olamine)

The originator company developed Revolade® (eltrombopag olamine) to treat certain patients with thrombocytopenia in chronic immune thrombocytopenic purpura and chronic hepatitis C infection. They held two patents: IN213176, which covered eltrombopag as a composition of matter and expired on May 24, 2021, and IN233161, which covered the olamine salt of eltrombopag and expired on May 21, 2023. Before the IN'161 patent expired, Natco had launched Trombopag®. The originator company filed lawsuits at the Delhi High Court against Natco and obtained a preliminary injunction on December 13, 2021, that blocked Natco's generic activity. The interim injunction obtained by the originator company was a tactic to delay the availability of a more affordable treatment option, thereby prioritising profits over patient access. When Natco appealed the preliminary injunction, the Division Bench set it aside on April 24, 2024. As a result, Natco was restrained from December 13, 2021, until the '161 patent expired, a decision that was ultimately overturned by the Division Bench. The originator company then appealed this decision to the Supreme Court. On August 2, 2024, the Supreme Court set aside both the preliminary injunction and the Division Bench's decision.

Trajenta® (linagliptin)

An originator company markets Trajenta® (linagliptin) and Trajenta Duo® (linagliptin; metformin) for the treatment of type 2 diabetes mellitus. The originator company held two patents – the genus patent IN227719 (IN'719) that covered linagliptin generically and expired on February 21, 2022 and the species patent IN243301 (IN'301), which covered linagliptin specifically as a compound and expired on August 18, 2023.

In 2022, the originator company initiated multiple patent infringement lawsuits against generic companies in two different High Courts, namely the Delhi High Court and the Himachal Pradesh High Court. From February 2022 to June 2022, the Himachal Pradesh High Court issued preliminary injunctions in a patent infringement case against a few generic companies. These injunctions prevented these companies from manufacturing and selling generic products containing linagliptin. Subsequently, the generic companies filed appeals before a Division Bench of the Himachal Pradesh High Court to challenge the injunctions. However, these appeals were dismissed in March 2024 following the expiration of the linagliptin patent in August 2023.[147]

Interestingly, in a parallel case, the Delhi High Court reached a different outcome in March 2023 by rejecting the originator company's request for preliminary injunctions against some generic companies. The Court also opined that the patent was likely going to be revoked on the grounds of prior claiming and stressed that "*by filing multiple patent claims in respect of the same invention, the plaintiffs have made an attempt towards evergreening the invention and re-monopolizing the same. These attempts on behalf of the patentees strike at the root of patent law in India. The aforesaid conduct of the plaintiffs defeats the rights of the manufacturers of generic drugs such as the defendant companies and is also detrimental towards the public interest*."

Additionally, the court ordered the originator company to compensate the generic companies financially. The originator company subsequently appealed this decision to a two-judge Division Bench of the Delhi High Court. However, in February 2024, the Division Bench dismissed the appeals as IN'301 had expired by that time. Furthermore, the Division Bench ruled that any determination regarding the costs incurred during the preliminary injunction proceedings would await the final decision in the infringement lawsuits.

As a result of the preliminary injunction strategy employed by the originator, generic companies were prevented from launching affordable and accessible medicinal products from February 22, 2022, until March 29, 2023.

[147] CS(COMM) 239/2019; CS(COMM) 240/2019; CS(COMM) 236/2022, CS(COMM)237/2022 and CS(COMM) 238/2022.

Patent issues

Sham litigations

1.5. Sham litigations

Sham or vexatious litigation is the practice put in place by companies that file claims before a court not to assert their rights but merely to harass the opposing party, as part of a plan to eliminate competition. As stressed in the 2020 WTO-WIPO-WHO Trilateral Study, "*[u]nder this strategy, a patent holder brings a patent infringement suit that is "objectively baseless", the sole purpose of which is to create costs and delays to market entry for a prospective competitor*".[148]

1.5.1. Brazil

The Draft Law February 2023 makes it an infringement of the economic order to abuse the right to petition or take legal action with the aim of causing economic damage to rival companies. Already approved by the Senate, the text is now before the Chamber of Deputies in Brazil. The proposal amends the Competition Defence Law (Law n° 12.529/2011). The aim of the Draft Law is to include sham litigation among anti-competitive practices. Notably, the Administrative Council for Economic Defence, the competition defence agency, already has the power to punish this type of abuse, but the text makes the law clearer, increasing legal certainty.

Sham litigations nevertheless take place in Brazil. This is evidenced by a case in which the Administrative Council for Economic Defence fined a global pharmaceutical company for filing sham litigations against generic companies.

A global pharmaceutical company

The Administrative Council for Economic Defence fined a global pharmaceutical company approximately 8.4 million USD in June 2015 for filing sham litigation claims. According to the Administrative Council for Economic Defence, the company actions met the three requirements necessary for establishing sham litigation according to Brazilian case law:

a) implausibility of the claims;
b) provision of erroneous information; and
c) unreasonableness of the means used.

The Administrative Council for Economic Defence noted that the originator company managed to keep generic companies out of the market between 2007 and 2008. As a result of the sham litigation, São Paulo's health department paid three times more for the medicinal product in question in comparison with the period prior to patent expiry.

[148] 2020 WTO-WIPO-WHO Trilateral Study "Promoting Access to Medical Technologies and Innovation", p. 272.

1.5.2. Canada

Sham litigations take place in Canada. This is clearly demonstrated in the context of Dexilant® (dexlansoprazole).

Dexilant® (dexlansoprazole)

The originator company pursued patent infringement against Apotex in respect of the medicinal product Dexilant® (dexlansoprazole), a proton pump inhibitor, on the basis that the generic product would infringe two patents. The first patent was dropped before trial but the second patent, claiming a pulsatile capsule formulation comprised of two sets of beads to be released at different times, was prosecuted through trial.[149]

It was plain that the generic product was not a pulsatile formulation but rather a formulation that released the medicinal product in a single, continuous delayed release fashion. Notwithstanding this, the originator company pursued the action through trial and was entirely unsuccessful. The trial judge found, amongst other things, that the originator company did not lead evidence of an expert pertinent to the patent and that there were serious concerns with the expert evidence that the originator company did lead, and accorded limited weight to them. The court observed that the originator company's experts did not even read the whole of Apotex's expert reports, nor did they read the prior art, relying instead on what was told to them by counsel. Indeed, the trial judge found that the originator company's second expert's evidence on the prior art was tainted by the select reading taken, thereby putting the impartiality and independence of his opinions in question. As a consequence, the trial judge dismissed the action and granted Apotex a significant legal costs award. Understandably, the originator company did not appeal.

1.5.3. European Union

A pertinent example of sham litigations in the European Union relates to NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring).

NuvaRing® (etonogestrel/ethinyl estradiol vaginal ring)

In October 2022 the Spanish Competition Authority fined an originator company 39 million EUR for abusing the legal system with the sole purpose of eliminating competition and securing the exclusivity in the market of their Nuvaring® product, a vaginal ring to prevent pregnancy.[150]

The Spanish Competition Authority concluded that the *ex parte* preliminary injunction proceedings and the previous legal actions (discovery proceedings) the originator company enforced against León Farma and Exeltis Healthcare back in 2017 were all unfounded and abusive. Unfounded because the originator company already knew that the Leon Farma/Exeltis vaginal ring did not infringe their Nuvaring product and they had no single evidence showing the contrary; abusive because they hid that information, manipulated the experts and misrepresented in court to get an injunction against León Farma/Exeltis that affected the launch on the European market of the innovative and non-infringing vaginal ring manufactured in Spain by León Farma.

[149] Takeda v. Apotex, 2024 FC 106.
[150] See https://www.cnmc.es/prens/multa-merck-20221025 .

Patent quality

2. Patent quality

As shown in 0 regarding patent issues, ensuring the highest possible quality of patents is essential for the patent system and healthcare generally. The quality of patents ensures that they serve their purpose of promoting innovation, and contributing to fostering technological, social and economic development. Drafting a patent application is a rigorous exercise in technical language that must accommodate the technology underlying the invention, its commercial significance, and relevant legislation and jurisprudence. Patent examiners, who read the applications and ultimately decide whether to grant a patent, must have a sound understanding of these and other factors, in order to ensure the quality of the patent examination procedure.

The importance of ensuring a high quality patent granting system is stressed in the 2020 WTO-WIPO-WHO Trilateral Study: *"[e]rroneously granted patents may lead to costly litigation and delay entry of generic versions, thus negatively impacting access to medicines"*.[151] For these reasons, there exist safeguards aiming at ensuring the highest possible quality of the patent granted and of the granting procedures, such as, for instance, pre-grant opposition mechanisms in the course of the granting procedure. A thorough examination of the validity of patents avoids court invalidations of granted titles, which undermines the credibility of intellectual property systems necessary for innovation and competition. This study shows that the more sophisticated the patent systems are, the more sophisticated the patent strategies become, thereby requiring more sophisticated patent quality guardrails.

2.1.1. Argentina

The "Guidelines for Pharmaceutical and Biotechnological Inventions"[152], the possibility to file observations, and the judicial challenge to the validity of a patent after it is granted, ensure the quality of patent examination, and, therefore, patent quality. The Argentina Patent Office performs substantive examination of patent applications according to the Argentina Patent Act. Even though the Argentinean Patent Office has budget constraints that limit the number of patent examiners and resources, in the pharmaceutical field, the Guidelines guarantee patent examination quality. These Guidelines have proven to be an effective tool to prevent evergreening, making it easier to launch generic and biosimilar products in Argentina.

In addition to the Guidelines, the Argentina Patent Act allows filing of observations during patent prosecution. According to this procedure, any individual may submit evidence to the Argentinean Patent Office demonstrating that a patent application fails to meet patentability criteria. The Argentinean Patent Office will add such submissions to the patent application file and may consider them when deciding whether to deny or grant the patent. Once the patent is granted, the Argentina Patent Act establishes a cause of action to challenge its validity before the Federal Courts. The Act does not provide an administrative

[151] 2020 WTO-WIPO-WHO Trilateral Study "Promoting Access to Medical Technologies and Innovation", p. 232.
[152] Joint Resolution No. 118/2012, 546/2012 and 107/2012, Adoption of Guidelines for the Examination of Patent Applications of Chemical and Pharmaceutical Inventions, Ministerio de Salud [Ministry of Health], Ministerio de Industria [Ministry of Industry], and Instituto Nacional de la Propiedad Industrial [Industrial Property National Institute], B.O., May 8, 2012.

pre-grant or post-grant opposition system. The judicial procedure is lengthy and costly, and it allows for a wide-ranging debate and presentation of evidence.

Cámara Industrial de Laboratorios Farmacéuticos (CILFA), the primary and leading association for generic and biosimilar companies in Argentina, has actively filed observations to patent applications since 2003, with a total of 461 observations by 2023. Among these, 458 applications have either been refused, abandoned, or withdrawn by the applicants, the Argentina Patent Office only granted three of these applications (0.65%). Therefore, observations during prosecution been a highly effective mechanism to avoid evergreening practices.

2.1.2. Brazil

In Brazil, the quality of patents can be monitored through the administrative examination process, following the National Institute of Industrial Property's Examination Guidelines, and through competitors, either through the filing of examination subsidies, provided for in Article 31 of Law No. 9.279/96, or through the Administrative Nullity Process, provided for in Article 51, within a period of six months from the grant of the patent.

The examination subsidies and administrative nullity proceedings filed by competitors help the examiners to visualise matters that may not be new or inventive through patent and non-patent literature. Examiners are obliged to mention and respond appropriately to the allegations of subsidies and invalidations, and the examination is often reviewed by a collegiate body, thus improving the quality of the patents that are granted.

2.1.3. Canada

Patent quality and the quality of the patent examination procedure in Canada are provided by the examination of the application by the Canadian Intellectual Property Office, the availability of post-grant re-issuance and re-examination, and through challenges to the validity of a patent before the Federal Court of Canada.

The Canadian Intellectual Property Office performs a substantive examination of patent applications, and is a receiving office, international search authority, and international preliminary examination authority for applications filed under the Patent Cooperation Treaty. The Canadian Intellectual Property Office participates in numerous patent prosecution highway (PPH) agreements through both a global PPH or individual bilateral agreements to expedite patent prosecution where a corresponding application has been allowed by a participating PPH partner.

Canada does not have a pre-grant opposition mechanism. However, pre-grant, any person may, pursuant to Section 34.1 of the Patent Act, file prior art believed to have a bearing on the patentability of any claim in an application, along with a written communication, pursuant to Section 12 of the Patent Rules, explaining the relevance of the prior art, for consideration by the patent examiner. However, the outcome of such protest is entirely at the discretion of the Examiner. In other words, the protestor does not have any control over the procedure after having submitted the prior art and protest.

Canada does not have a post-grant opposition procedure. However, any person has the ability to request that a patent be re-examined by submitting prior art and an explanation of its relevance to the patent office. The patentee is involved in the re-examination proceedings, comments on the prior art and responds to communications from the Patent Appeal Board. However, a third party that filed the request for re-examination is not part of the re-examination proceedings. Because third parties are not part of re-examination proceedings, such proceedings are rarely used in Canada. Post-grant challenges to the validity of a patent in respect of prior art or other issues are adjudicated by the Federal Court of Canada.

Canada offers a Certificate of Supplementary Protection for certain patents claiming an eligible medicinal ingredient or combination of eligible medicinal ingredients. A Certificate of Supplementary Protection provides patent-like

protection for up to two years beyond an original patent term depending on the amount of time between the filing date of the patent and the approval of the medicinal product in Canada. There is no mechanism for the pre- or post-grant challenge of a Certificate of Supplementary Protection granted by Health Canada. However, as with patent validity, the validity of a Certificate of Supplementary Protection may be challenged before the Federal Court of Canada.

2.1.4. India

In order to avoid the granting of low-quality patents, the Indian Patent Act allows challenges to pending patent application and granted patent by filing an opposition before the patent office. These oppositions take the form of either pre-grant oppositions, which may be lodged by any person prior to patent grant, or post-grant oppositions, which may be initiated by any interested party subsequent to patent grant but within one year from the date of publication of such grant. The primary objective of a pre-grant opposition is to facilitate the consideration of pertinent prior art by the patent examiner prior to the issuance of a patent. In other words, the pre-grant opposition mechanism serves as a valuable tool in facilitating the examination process of patent applications and ensures the quality of patent while filtering out non-patentable applications. It has been a successful process, and several non-genuine patent applications have been rejected by the patent office.

As outlined in the Annual Report for the fiscal year 2021-2022[4] from the Office of the Controller General of Patents, Designs, Trademarks, and Geographical Indications, key statistics regarding patent publications and instances of pre-grant oppositions were disclosed. For instance, the Indian Pharmaceutical Alliance has been actively monitoring patent applications since 2009, with a total of 1870 oppositions recorded as of 2023. Among these, 1195 applications have either been refused, abandoned, or voluntarily withdrawn by the patentee, with only a handful of cases proceeding to appeal. This trend suggests that the originator companies themselves discerned the lack of novelty in these applications, leading them to forego pursuing patent protection. Many of these applications appear to be efforts aimed at evergreening, but when confronted, they often ceased to be pursued further. This highlights the efficacy of the pre-grant opposition process in maintaining patent quality and curbing unjust monopolies.

The case relating to Glivec® (imatinib) stands out as a landmark decision for its impact on preventing evergreening in the pharmaceutical industry in India.

Glivec® (imatinib)

The originator company applied for a patent (1602/MAS/1998) for the beta crystalline form of imatinib mesylate, which is used to treat leukaemia. The original molecule patent on imatinib, with an April 1992 priority date, was not filed in India due to the absence of provisions for product patents at that time.

The Indian Patent Office rejected this application, citing Section 3(d) of the Patents Act, 1970, which prevents patents for new forms of known substances unless they show "significantly enhanced efficacy". This section

aims to limit patents to discoveries that significantly improve on known substances in terms of efficacy, including therapeutic outcomes.

Section 3(d) reads as follows:

> *3. What are not inventions.—The following are not inventions within the meaning of this Act,—*
>
> *(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*
>
> *Explanation.— For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;*

The core issue in this case was how "efficacy" was defined and interpreted. The originator company contended that the improved bioavailability of the beta form constituted enhanced efficacy. However, the Supreme Court, led by Justice Aftab Alam, offered a strict interpretation, equating "efficacy" with therapeutic efficacy, meaning a demonstrable improvement in health outcomes. The originator company could not prove that the beta form offered a significant improvement in therapeutic efficacy, leading to the rejection of their patent application.

This decision was pivotal in setting a high standard for the patentability of modifications of medicinal products in India and acted as a significant deterrent against evergreening practices. This landmark ruling has underscored the importance of balancing innovation with public health and access to affordable medicinal products. It sends a clear message that patents should be granted for genuine therapeutic advancements and has influenced patentability criteria in developing countries, emphasising public health and access to medicinal products. The Glivec case has become a critical precedent for future cases involving the patentability of new forms or modified versions of known medicinal products, demonstrating the effective use of Indian Patent Law to ensure that life-saving medicinal products remain accessible and reasonably priced. [153]

2.1.5. European Union

Patent quality and quality of patent examination procedures is a very debated topic in the European Union. There is cross-sectoral concern about the deteriorating patent quality of the European Patent Office. This is due to, amongst others, the working environment for the examiners and the lack of time they have for thorough search and examination.[154]

Among the safeguards foreseen in the granting procedures before the European Patent Office to ensure patent quality are third party observations - which however result having a very limited value in the actual examination - and post-

[153] Novartis Ag vs Union Of India & Ors on 1 April, 2013, Supreme court of India, Judgement in Civil appeal no. IN 2706-2716 OF 2013 with Civil appeal No. 2728 OF 2013 and Civil appeal Nos. 2717-2727 OF 2013.
[154] See https://patentblog.kluweriplaw.com/2023/02/11/concerns-about-deteriorating-patent-quality-at-the-epo/.

grant oppositions - which however are not a very effective mechanism for preventing the enforcement of invalid patents. Very often, the examiner examines an application thoroughly, but eventually, after a consultation by telephone, he grants the patent for reasons which are not published. The grant of a patent often lacks transparency.

The debate around quality of patents in the European Union has extended recently to supplementary protection certificates. The European Commission recently proposed legislation on the Unitary Supplementary Protection Certificate and centralized procedure for granting national supplementary protection certificates[155] that include a pre-grant opposition mechanism, introduced in the proposed legislation to guarantee the highest quality of the supplementary protection certificates granted.

A pre-grant opposition mechanism is an essential part of the supplementary protection certificate proposal of the European Commission and is strongly supported by the European Parliament as it intends to prevent invalid (non-innovative) supplementary protection certificates from being enforced via strategic litigation and ultimately invalidated in the court with distortions of competition, delaying access to generic and biosimilar products, as experienced recently for HIV and multiple other essential medicinal products.

As for patents, it would be essential and in the interest of all stakeholders to ensure a thorough examination of supplementary protection certificates during the granting process rather than after they are granted. This would ensure that only high quality (i.e. legitimate) supplementary protection certificates are granted and would avoid litigation strategies to delay competition, which commonly occur under today's legal system. The impact of this problem is clearly identified, among others, in the context of Truvada® (emtricitabine and tenofovir); Janumet® (sitagliptin and metformin); Xalatan® (latanoprost); and Prezista® (darunavir).

Truvada® (emtricitabine and tenofovir)

The illegitimate supplementary protection certificate on Truvada® (emtricitabine and tenofovirdisoproxil), a medicinal product that reduces HIV transmission by over 90%, was invalidated everywhere across the European union and ultimately declared illegitimate by the European Court of Justice. However, due to longer court procedures in some countries, like Portugal, generic versions were delayed, leaving 95.000 patients without HIV or preventive treatment and creating additional costs for the Portuguese healthcare system of 109 million EUR (equivalent to 1.1% of total 2018 health budget). Similar delays occurred in Italy.

Janumet® (sitagliptin and metformin)

The illegitimate supplementary protection certificate on Janumet® (sitagliptin and metformin), a medicinal product used for type 2 diabetes, had been invalidated in some Member States (e.g. Germany), but due to long court procedures (never taking a decision) in other countries, and patent linkage in Italy, blocked generic reimbursement, delaying competition in Italy in 2023 by six months, costing the Italian healthcare system at least 9.8 million EUR.

Xalatan® (latanoprost)

In January 2024, a fine of 13 million EUR for the originator company was confirmed by the Italian Supreme Court for an anti-competitive strategy delaying generic entry by seven months by using the supplementary

[155] See https://single-market-economy.ec.europa.eu/publications/proposals-regulations-supplementary-protection-certificates_en.

protection certificate and the unlawful patent linkage system (i.e. blocking the generic company's pricing and reimbursement procedure) on Xalatan® (latanoprost), a critical medicinal product for eye glaucoma.

Prezista® (darunavir)

A pre-grant opposition procedure could have prevented numerous and complex national court proceedings on some questionable supplementary protection certificates such as Prezista® (darunavir) for HIV prevention and treatment, invalidated by the Dutch, Spanish and Swedish Courts, or for Tecfidera® (dimethyl fumarate), where the Dutch patent office took a different stance on the supplementary protection certificate from other patent offices.

2.1.6. Mexico

Patent quality in Mexico is frequently poor. The current administration under President Andres Manuel López Obrador advocates for what it terms as "Republican Austerity". This approach, which includes maintaining or even reducing budgets in government offices, could potentially hinder the enhancement of human and material resources necessary for the examination and improvement of patent quality.

In addition to the terrible effect of poor-quality patents, Mexico is experiencing a new major problem regarding the legal standing required to nullify invalid patents. About three years ago, the Mexican Institute of Industrial Property made a radical change in the concept of legal standing. Prior to this twist, any pharmaceutical company could request the invalidity of an improperly granted patent with the sole fact of proving that it belonged to the industry. With the change in the Mexican Institute of Industrial Property criterion, it is now necessary to prove that the patent constitutes a real and actual harm. Unfortunately, this criterion was validated by the Specialized Chamber on Intellectual Property and afterwards by one of the two chambers of the Supreme Court of Justice of the Nation (Second Chamber). There are still some pending cases in the First Chamber. It is still uncertain whether this Chamber will follow the same criterion as the Second Chamber or will put a new slant on the interpretation of the Article of the Industrial Property Law relating to the particular legal qualifications necessary to start a nullity action proceeding. The practical impact of this rule is that until a generic or biosimilar company has approval for a medicinal product, it cannot challenge the validity of any patent which might block it from launching that product. When combined with the patent linkage scheme in Mexico that will not allow grant of approval to a generic or biosimilar product until all relevant patents have expired, it is expected that the launch of generic and biosimilar products in Mexico will be seriously delayed.

The Federal Law for the Protection of Industrial Property, in force since November 5, 2020, does not stipulate an opposition system *per se*, but the possibility for any person to provide the Mexican Institute of Industrial Property with information regarding whether the application meets the patentability requirements. The time limit for the third party to provide relevant information is only two months after the publication of the patent application.

Regulatory and non-patent issues

Product hopping

3. Regulatory and non-patent issues

3.1. Product hopping

Product hopping refers to the introduction by originator companies of modified versions of medicinal products or second-generation medicinal products and the strategies used to switch patients from a reference product to a follow-on product that benefits from further patent protection. This may include the complete removal from the market of the original formulation. The removal effectively forces all patients to switch to another notionally "improved" formulation, for example, the introduction of a tablet in place of a capsule, that happens to be patent protected for a longer period of time. As stressed in the 2020 WTO-WIPO-WHO Trilateral Study, product hopping "*is a strategy applied by patent holders when products are nearing patent expiry*".[156]

The second-generation medicinal product may be more expensive leading to an immediate increase in profits. The first-generation medicinal product may be withdrawn entirely, forcing clinicians to prescribe the more expensive second-generation product (so called "hard switch"). Alternatively, the market for the first-generation product may be left to atrophy, whilst all marketing and promotional spend is focused on moving sales on to the second-generation product (so called "soft switch").[157] A successful switch will ensure the product market retains patent protection for a longer period of time, as the market for the first-generation product has effectively been eliminated prior to market entry of generic or biosimilar companies. A generic or biosimilar company seeking to bring a generic or biosimilar version of the first-generation product to market will find that all patients have already been established on the second-generation product. Issues such as prescriber inertia inhibit switching back to the first-generation product even though a generic version of equivalent therapeutic value may now be available at a lower cost. The second-generation product will be established as the incumbent product of choice. The fact it also benefits from patent or regulatory exclusivities effectively neutralises all the potential benefits of generic or biosimilar competition.

3.1.1. European Union

Pertinent examples of product hopping within the European Union can be identified in the context of Losec® (omeprazole) where the European Commission found that the originator company had abused its dominant position, and in the context of Coversyl® (perindopril) where the European Commission concluded that the originator company used product hopping as an evergreening strategy.

Losec® (omeprazole)

In 2005 the European Commission found that an originator company had abused its dominant position through, amongst other things, the launch of a tablet form of Losec® combined with the deregistration of the marketing authorisations for the capsule form of Losec® in national markets where the patent or supplementary protection certificate was due to expire, and withdrawal of those capsules. The originator company was therefore fined 60 million EUR by the European Commission for misusing the patent system and adopting marketing strategies between 1993 and 2000 with the purpose of delaying market entry of generic companies.[158]

[156] 2020 WTO-WIPO-WHO Trilateral Study "Promoting Access to Medical Technologies and Innovation", p. 274.
[157] https://www.ftc.gov/system/files/ftc_gov/pdf/p223900reportpharmaceuticalproducthoppingoct2022.pdf.
[158] European Commission's decision of 15 June 2005: https://ec.europa.eu/commission/presscorner/detail/en/IP_05_737.

This finding was appealed and upheld by the European Courts.[159] The European Courts found that the deliberate deregistration of the marketing authorisation was designed to hinder the introduction of generic products and parallel imports and, therefore, could not be considered competition on the merits.[160] Internal documents evidenced the originator company's underlying intent and failed to demonstrate its arguments at trial that it had legitimate reasons for deregistration.[161]

While it was acknowledged that the originator company had a right under law to request the withdrawal of its marketing authorisation, this did not prevent such conduct also being an abuse of the originator company's dominant market position, and it was noted that the majority of cases concerning the abuse of a dominant position consisted of behaviour that would otherwise be lawful under other branches of law.[162] Indeed, the evidence found by the European Commission during its investigation of the case left no doubts as to the strategic intentions of the originator company, which were expressly mentioned in their internal communications, i.e. "*delay generic introduction through technical and legal hurdles" because "[e]very day of protected sales of Losec® is worthwhile considering the huge sales volume projected at patent expiry*".[163]

It should be noted that in this case, the abuse and commentary surrounding it primarily related to the originator company's withdrawal of the marketing authorisation in certain jurisdictions for the capsule form of Losec®. At the time, this prevented generic companies from relying on it for their own marketing authorisations. Such activity would no longer prevent a generic company from relying on it[164] due to the subsequent introduction of the concept of global marketing authorisation in the European Union and, therefore, this aspect of the originator company's abusive behaviour would no longer impact competition.

Coversyl® (Perindopril)

In an investigation into the originator company's perindopril product, used to treat hypertension, the European Commission found in 2014 that the originator company had a strategy of switching patients from its first-generation perindopril product to its second-generation perindopril product, which had obtained patent protection until 2023. The originator company then withdrew the first-generation product before generic companies could enter the market. The European Commission noted that *"[d]epending on the national regulatory regime, generic substitution was made impossible or limited. It is undisputed that the second-generation product has no therapeutic advantages for patients over the first-generation product*".[165] This strategy was confirmed by the Court of Justice of the EU in 2024.

In addition, there are several ongoing cases and investigations relating to product hopping in the European Union in the context of MabThera®, Rituxan® (rituximab) and Herceptin® (trastuzumab). These cases clearly demonstrate the significant impact of product hopping on the healthcare budgets in the European Union.

[159] AstraZeneca AB and AstraZeneca plc v European Commission, C-457/10 P, para. 129.
[160] Ibid 130.
[161] AstraZeneca, OJ 2006 L332/24, para. 789 and AstraZeneca AB and AstraZeneca plc v European Commission, C-457/10 P, para. 136.
[162] AstraZeneca AB and AstraZeneca plc v European Commission, C-457/10 P, para. 132.
[163] Commission Decision of 15 June 2005 relating to a proceeding under Article 82 of the EC Treaty and Article 54 of the EEA Agreement (Case COMP/A. 37.507/F3 ñ AstraZeneca), para 271. Available at: https://ec.europa.eu/competition/antitrust/cases/dec_docs/37507/37507_193_6.pdf.
[164] European Commission, Final Report: Pharmaceutical Sector Inquiry (8 July 2009), para. 1041 (https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf).
[165] AT.39612 – Perindopril (Servier), (2014) para. 8.

MabThera® (rituximab) and Herceptin® (trastuzumab)

Secondary patents in Poland covering rituximab and trastuzumab, two critical oncology products, despite already being revoked in all other European jurisdictions, were challenged and litigated in the court for several years in Poland. Once the molecule patents were about to expire, the patent landscape allowed the originator company to gradually switch patients from intravenous to subcutaneous administration of the two products, significantly delaying access to intravenous biosimilar products in Poland.

According to the Polish National Health Fund, the annual cost for the reimbursement of rituximab and trastuzumab was around 48 million EUR and 70 million EUR respectively. The savings lost due to the introduction of the subcutaneous forms was estimated from over 41 million EUR in one year to over 56 million EUR in three to four years from the introduction of the biosimilar products.

Similarly, in the Netherlands, once the trastuzumab patent was about to expire, the originator company switched patients from an injectable version to a subcutaneous version of the medicinal product in order to reduce the impact of the market entry of biosimilar products.

In a detailed study on the impact of these evergreening strategies on trastuzumab in the Netherlands, it was calculated that *"the costs for subcutaneous Herceptin® substantially decrease with the introduction of the biosimilars. […] [T]he average cost of trastuzumab in the biosimilar period is about 48% lower than in the patent period, in 2020 even 57%. After the introduction of the biosimilars also the costs of subcutaneous Herceptin® (still under patent) substantial dropped, however, the drop in costs is about 34%"*.[166] In addition to significantly delaying patient access to biosimilar treatment, the study confirmed that if biosimilar competition were not delayed and "*all treatments were substituted with biosimilars […] €4.1 million could have been saved on drug expenditures in the period June 2018 until December 2020*" in the Netherlands only.[167]

[166] See Kirshner, G., Makai, P., Brouns, C. et al. The impact of an 'evergreening' strategy nearing patent expiration on the uptake of biosimilars and public healthcare costs: a case study on the introduction of a second administration form of trastuzumab in The Netherlands. Eur J Health Econ (2024). https://link.springer.com/article/10.1007/s10198-023-01648-w.

[167] See Kirshner, G., Makai, P., Brouns, C. et al. The impact of an 'evergreening' strategy nearing patent expiration on the uptake of biosimilars and public healthcare costs: a case study on the introduction of a second administration form of trastuzumab in The Netherlands. Eur J Health Econ (2024). https://link.springer.com/article/10.1007/s10198-023-01648-w.

3.1.2. India

Product hopping occurs through various reformulation strategies. Notable categories include (a) new dosage forms – transition from one dosage form (e.g. capsule, tablet, injectable, solution, suspension, or syrup) to another, (b) molecule modifications such as enantiomer switch, and (c) combination of previously marketed individual products. The essence of this practice lies in compelling patients to switch from their existing medicinal products to other medicinal products within the same therapeutic category, which is equivalent to the medicinal product they were using earlier. Doctors are encouraged to prescribe the reformulated medicinal product instead of the original product. This shift redirects prescriptions from the cheaper original versions of the medicinal product to costlier reformulated medicinal products, which might have additional patent protection.

A few examples of product hopping are related to the medicinal products in the table below:

Initial first line Product	New / Reformulated Product
Palbociclib Capsule	Palbociclib Tablet
Tamsulosin Capsule	Tamsulosin & Dutasteride Capsule

3.1.3. Middle East and North Africa

In the Middle East and North Africa, there are many examples of product hopping, including, amongst others, in the context of Ibrance® (palbociclib).

Ibrance® (palbociclib)

Palbociclib is sold under the brand name Ibrance® by the originator company for treatment of breast cancer. In 2015, this medicinal product was approved in the U.S. in capsule dosage form. In late 2019, a new dosage form (tablet) was approved with the same strengths. We believe that the market share in the Middle East and North Africa will be shifted from capsule dosage form to tablet dosage form.[168]

In the Middle East and North Africa, the product patent for palbociclib was filed in the Gulf Cooperation Council, Algeria, Egypt, Tunisia, Morocco and Lebanon and expired on January 20, 2023. No formulation patent related to the capsule dosage form was filed in Middle East and North Africa. In 2016, a formulation patent application eq. to WO2016193860 was filed in Algeria, Bahrain, Egypt, Kingdom of Saudi Arabia, Morocco, Oman, Qatar and the United Arab Emirates mainly for the tablet dosage form with special excipients with an expiry date of May 24, 2036.

[168] See https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process.

3.1.4. United Kingdom

In the United Kingdom, product hopping is a strategy that is used often by originator companies. Product hopping is, for instance, identified in the context of Priadel® (lithium carbonate) or Gaviscon® (sodium alginate, sodium bicarbonate, calcium carbonate).

Priadel® (lithium carbonate)

The Competition and Markets Authority launched an investigation on October 6, 2020, under Chapter II of the Competition Act 1998 into potential "abuse" of a dominant position by the originator company. This relates to the originator company's intention to discontinue the supply of Priadel®, a lithium carbonate medicinal product, for the treatment of bipolar disorder. The allegation was that the withdrawal of Priadel® would force customers to switch to Camcolit®, a more expensive lithium carbonate treatment also sold by the originator company. The suggestion was that Priadel® 400mg is priced at 4.02 GBP while Camcolit 400mg costs 48.18 GBP. The originator company has agreed to continue to supply Priadel® while the investigation is ongoing.[169]

Following the competition investigation, in December 2020, the originator company committed to continue supplying Priadel® to the UK for a period of five years.[170]

Gaviscon® (sodium alginate, sodium bicarbonate, calcium carbonate)

In 2011 the UK Office of Fair Trading found that the originator company had abused its dominant position through the withdrawal and delisting of Gaviscon Original Liquid® from the National Health Service prescription channel in 2005. This withdrawal was made after the expiry of the patent, but prior to the publication of a generic name. This meant that following withdrawal, most prescriptions were instead written for Gaviscon Advance Liquid®, which was another version of the medicinal product still under patent protection.[171]

The Office of Fair Trading found strong evidence that the originator company's decision to withdraw Gaviscon Original® was to restrict competition and encourage switching to Gaviscon Advance®[172] and the timing of this withdrawal was deliberately intended to limit and deter competition from generic companies.[173] Furthermore, the Office of Fair Trading found evidence in the originator company's internal documents that the withdrawal was not economically viable (i.e. it expected to suffer material market share losses from implementing the strategy) and was likely to be loss-making in the first instance.[174] From this, the Office of Fair Trading concluded that there was no commercially rational reason to have employed the strategy and that other than seeking to exclude effective competition to its Gaviscon® product line, there would have been no logical reason for it to have implemented the strategy.[175] Ultimately, the originator company admitted infringing UK and European competition law and agreed to pay a penalty of 10.2 million GBP.

[169] CMA, 'CMA to investigate the supply of bipolar drug' (Press Release 6 October 2020) [https://www.gov.uk/government/news/cma-to-investigate-the-supply-of-bipolar-drug], accessed 14 October 2020.
[170] https://assets.publishing.service.gov.uk/media/5fdb73c18fa8f5148deb3005/Commitments_decision.pdf.
[171] Office of Fair Trading, Abuse of a dominant position by Reckitt Benckiser Healthcare (UK) Limited and Reckitt Benckiser Group plc, Decision No. CA98/02/2011 (2011).
[172] Reckitt Benckiser, paras. 6.8 and 6.9.
[173] Reckitt Benckiser, paras. 6.14 and 6.23.
[174] Reckitt Benckiser, paras. 6.30.
[175] Ibid.

3.1.5. United States

There have also been a number of instances where allegations of product hopping have been considered by different courts in the United States. This has been the case, for instance, in the context of Tricor® (fenofibrate); Namenda® (memantine); and other medicinal products.

Tricor® (fenofibrate)

Over more than a decade, the originator company produced several bioequivalent formations of fenofibrate, already in generic form. Through a complex switching approach involving the sequential launch of branded reformulations (not superior to the first-generation product) and patent litigations to delay the approval of the generic companies, the manoeuvres were estimated to cost the U.S. healthcare system approximately 700 million USD a year. Historically, when patients are forced to switch from a medicinal product with a near-to-expiry patent to the new formulation, only 10% to 20% go back to the generic product once it becomes available.

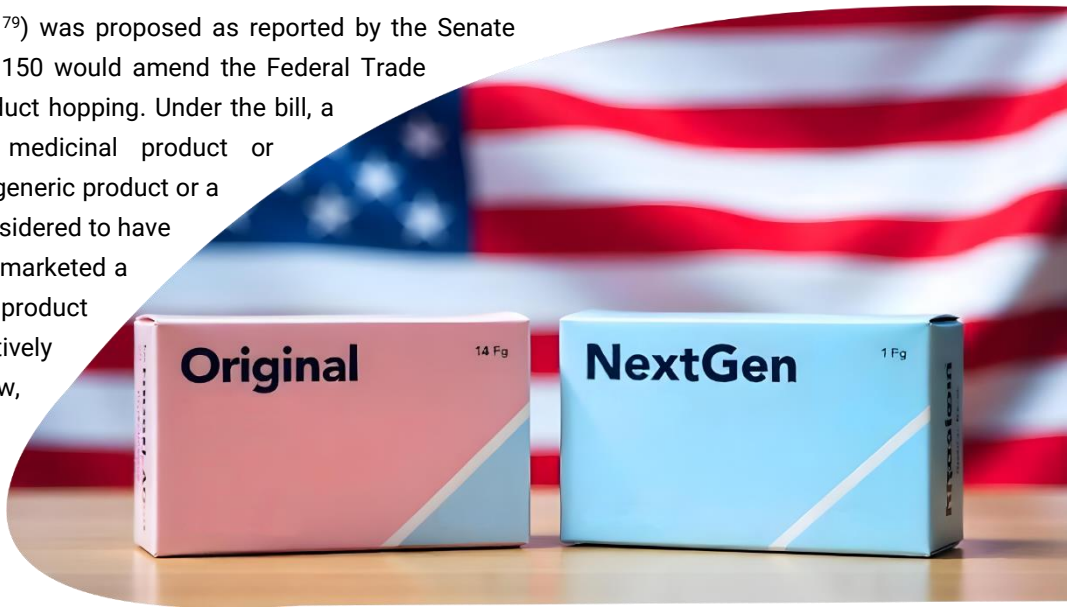
Namenda® (memantine)

The originator company attempted to remove an older version of Namenda®, a 1.5 billion USD medicinal product used to treat Alzheimer's disease, with a "new and improved" version (taken once daily instead of twice daily) that was protected by a patent until 2029. This product hopping scheme would have led to consumers paying almost 300 million USD more, third-party payors paying almost 1.4 billion USD more, and Medicare and its beneficiaries paying a minimum of 6 billion USD over the next ten years. Although the New York Attorney General obtained an injunction that prevented the originator company from removing the older version from market, other courts have allowed product hopping schemes to continue.[176]

Similarly, for another medicinal product, an originator company twice changed its product formulation (through marginally lowering the medicinal product's strength and changing from capsule to tablet), stopped supplying the older versions and took active steps to change the code in the National Drug Data File for the older versions to be obsolete, in effect preventing pharmacists from filling prescriptions with a generic version of these older medicinal products.[177]

A court found that by removing the old medicinal products from the market and changing the code in the National Drug Data File, consumer choice was removed, such conduct was considered "consumer coercion" and was "potentially anticompetitive".[178] The claim was settled by the parties.

[176] Jones H. G, and others, 'Strategies that delay or prevent the timely availability of affordable generic drugs in the United States 127(11) (2016) Blood, 1398 – 1402.
[177] Abbott Laboratories v. Teva Pharmaceuticals USA, Inc. (TriCor) 432 F. Supp. 2d 408 (D. Del. 2006), Section IV A. This case was also cited in Walgreen Co. vs AstraZeneca 534 F.Supp. 2d 146 (D.D.C. 2008), where it was alleged that AstraZeneca had sought to engage in product hopping by withdrawing marketing support for its original product and aggressively marketing its newly reformulated product. This case was dismissed by the Court, as absent the withdrawal there was no loss in consumer choice and generics successfully gained 30% of the market.
[178] Abbot Laboratories v Teva Pharmaceuticals USA, Section IV A 4.



On 13 June 2024 a bill (S. 150[179]) was proposed as reported by the Senate Committee on the Judiciary. S. 150 would amend the Federal Trade Commission Act to prohibit product hopping. Under the bill, a manufacturer of an original medicinal product or biological product (that is, not a generic product or a biosimilar product) would be considered to have engaged in product hopping if it marketed a reformulation or other follow-on product to treat the same or substantively similar condition and withdrew, discontinued, or otherwise unfairly placed the original product at a competitive disadvantage to the follow-on product.

A manufacturer of an original medicinal product or biological product would be prohibited from product hopping once that manufacturer is notified that the Food and Drug Administration has received an application for a generic version of the medicinal product or a biosimilar version of the biological product. That prohibition would be lifted either three years after the manufacturer of the original medicinal product first markets the follow-on product or 180 days after a competing generic product or biosimilar product is first marketed, whichever is earlier.

S. 150 would establish a statutory framework under which the Federal Trade Commission could seek remedies from companies that engage in product hopping. S. 150 specifies the justifications that a manufacturer may use to defend against an accusation of product hopping; identifies the criteria that the Federal Trade Commission must meet to rebut any justifications; and affirms that the promotion of a follow-on product or the absence of promotion for an original product do not, on their own, amount to product hopping.

S. 150 would also limit the number of patents that a sponsor of an approved application for an original biological product (that is, the entity that submitted the application) may assert (that is, allege infringement of) against an applicant seeking Federal Trade Commission approval for a biosimilar version of the biological product. A patent would count against the limit only if it met two criteria: (i) The patent must claim exclusive rights to the biological product, a use of the product, or a method or product used in the manufacture of the product; and, (ii) Either the patent must have been filed more than four years after the original biological product was approved or the patent must claim exclusive rights to a manufacturing process that is not used by the sponsor of the original biological product.

[179] S. 150, Affordable Prescriptions for Patients Act of 2023.

Regulatory and non-patent issues

Pricing strategies

3.2. Pricing strategies

Originator companies often determine pricing strategies in order to maximise profitability. One of these strategies includes predatory pricing, which occurs when a dominant undertaking deliberately reduces its prices to a loss-making level for a short-term to discipline its existing competitors or foreclose the market to new entrants with a view to strengthening or maintaining its market power later on by way of the foreclosing effect of such predation. To that end, in broad terms, predatory pricing could be defined as the setting of prices at an unreasonably low level (below a cost parameter) by an originator company to induce a generic or biosimilar company to exit the market or to deter its entry or expansion.[180]

A dominant undertaking is also prohibited from entering into exclusive agreements with its customers. Behaviour which in effect encourages exclusivity has also been scrutinised. One of the key areas where such behaviour is seen is through rebates that require and/or encourage a customer to purchase all of their requirements from the dominant undertaking. It is common practice for pharmaceutical companies to negotiate discounts and/or rebates and these can be beneficial as they result in lower prices. However, competition law practice has also shown that rebates can be anti-competitive. For instance, a loyalty rebate conditional on customers purchasing more than 80% of their requirements from the dominant company may be anti-competitive if it excludes competitors from the market.

3.2.1. Argentina

Pricing strategies, such as predatory pricing, take place in Argentina. This evergreening strategy was used by an originator company in the context of MabThera® (rituximab).

MabThera® (rituximab)

In one of Argentina's most critical public tenders, the originator company set the price of its rituximab below its import costs. It was reported to the competition authority as predatory pricing by a competing company, Elea, offering a biosimilar product. The complaint was dismissed because the competition authority considered it appropriate to adopt a restrictive view in predatory pricing cases to promote aggressive price competition and safeguard public funds.

In 2020, the impact of the entry of the biosimilar version of Mabthera® in Argentina was estimated to result in annual savings of approximately 4.4 million USD, potentially reaching 7.8 million USD in savings in the case of complete substitution[181]. Attempts to limit the entry of the biosimilar product and/or hinder its growth can be explained by this significant impact.

[180] See https://www.concurrences.com/en/dictionary/predatory-pricing#:~:text=The%20concept%20of%20predatory%20pricing,on%20by%20way%20of%20the.

[181] Jorgensen N., Spitzer E., Macadam P., Denamiel JP., Hnatiw S., Torres R., Documento de posición: impacto económico de la introducción de productos biosimilares de Bevacizumab y Rituximab al Sistema de Salud Argentino, Buenos Aires, Centro de Evaluación de Tecnologías Sanitarias (CETSA), Universidad ISALUD, 2020.

3.2.2. European Union

Article 102 of the Treaty on the Functioning of the European Union prohibits "*any abuse by one or more undertakings of a dominant position within the internal market or in a substantial part of it*". This general prohibition is mirrored in the national law of European countries.

Key to this prohibition is the principle that dominant undertakings have a "*special responsibility*" not to impair competition through conduct falling outside the scope of competition on the merits. There have been numerous examples of where companies have been found to have breached this prohibition for different behaviours in different sectors. A key area of abuse has been through the imposition of unfair pricing practices, such as predatory pricing or anti-competitive rebates, in an attempt to exclude competition from the market in the long term.[182]

There are many cases in the European Union in which predatory pricing or anti-competitive rebates have been identified. This is the case, for instance, in the context of Humira® (adalimumab); Tarceva® (erlotinib); Herceptin® (trastuzumab); and Subutex® (buprenorphine). These cases clearly underline the significant impact on the European healthcare budgets as a consequence of pricing strategies applied by originator companies.

Humira® (adalimumab)

Between 2018 and 2019, the Dutch Authority for Consumers and Markets investigated the state of competition in the Dutch TNF-alfa inhibitors market (TNF-alfa inhibitors are biological medicinal products used for rheumatism, psoriasis and Crohn's disease).[183] This coincided with an article in *De Groene Amsterdammer* in March 2019 alleging that the originator company had used various tactics to keep lower-cost biosimilar versions of Humira® (adalimumab) off the market.[184]

The primary allegation was that the originator company had offered discounts of up to 89% to hospitals (which are responsible for the purchase of the medicinal product in the Netherlands) on the condition that they purchase the reference product for all patients.[185] For example, an alliance of hospitals treating 10% of Humira patients in the Netherlands, the Santeon group, had identified Amgen as a more attractively priced alternative medicinal product for its rheumatism treatment needs.

However, the originator company subsequently approached each group hospital individually, outbidding Amgen with an 85% price reduction.[186] The article concluded that the scheme had been successful overall, with

[182] For a broader overview of such evergreening strategies, see the European Commission's "Update on Competition Enforcement in the Pharmaceutical Sector (2018-2022)" available here.
[183] Authority for Consumers and Markets, Sector Inquiry: TNF-alfa Inhibitors (September 2019), p.2.
[184] Hordijk, L., 'Het patent gaat voor de patiënt', De Groene Amsterdammer (27 March 2019) [https://www.groene.nl/artikel/het-patent-gaat-voor-de-patient].
[185] Ibid.
[186] Ibid.

at least 70% of Dutch patients continuing to use the originator product at the time of publication, despite the availability of biosimilars with cheaper list prices.[187]

Tarceva® (erlotinib)

In January 2020, the Romanian Competition Council fined an originator company 3.4 million EUR for abusively implementing a strategy to prevent sales of cheaper alternatives to erlotinib. It was found that the originator company had been directing patients to their most expensive product and encouraging sales by covering the difference that patients paid between the expensive medicinal product and cheaper equivalents.

This was found to have cost the National Health Insurance Fund an additional 410,000 EUR in reimbursement costs compared to the cost if patients had chosen the cheaper equivalent medicinal products.[188]

Herceptin® (trastuzumab)

Between 2017 and 2019, biosimilar companies were blocked from participating in dozens of tenders for trastuzumab, used for treatment of chronic lymphocytic leukaemia, breast cancer, ovarian cancer, kidney cancer. The tenders were won by the originator company, which was selling its medicinal product to the other competitor distributors at a higher price than its own bid in the tender. This way, the originator company squeezed the wholesalers' margins and eliminated the competition in the auction. The originator company was therefore later fined by the Romanian Competition authority for distorting competition for biosimilar companies. The tenders were unduly restricted for several years, with huge costs for the Romanian healthcare system.[189]

The Romanian Competition Council fined the originator company 9,47 million EUR and besides the delayed patient access to more affordable treatment, it stressed that *"[t]his strategy implemented […] to delay the access on the market of biosimilar products affects the CNAS budget allocated to the national oncology program"* and led to lost savings of approx. 7.1 million EUR for the Romanian national healthcare budget.[190] The anti-competitive behaviour was confirmed in October 2024 by the High Court of Cassation and Justice.[191]

Subutex® (buprenorphine)

Following a complaint, the French competition authority investigated an originator company for abusing its dominant position and entering into an anti-competitive agreement with its supplier. Both of these findings related to a strategy by the originator company to prevent the generic version of Subutex® from successfully entering the market.[192]

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[187] Ibid.

[188] Consiliul Concurentei Romania, The Competition Council Sanctioned Roche Romania with Fines of 12.8 million Euro, (January 2020) http://www.consiliulconcurentei.ro/wpcontent/uploads/2020/04/amenda_roche_ian_2020_english.pdf . This case is well described at p. 27 of the European Commission Report "Update on Competition Enforcement in the Pharmaceutical Sector (2018-2022)" available here.

[189] This case is well described at p. 27 of the European Commission Report "Update on Competition Enforcement in the Pharmaceutical Sector (2018-2022)" available here.

[190] See: https://www.biosimilardevelopment.com/doc/the-competition-council-sanctioned-roche-romania-with-fines-of-million-euro-0001.

[191] See: https://mcusercontent.com/80a2795e9aa8aacac0c148b3b/files/4f2e2e80-6750-92cb-0fb6-b38e0e7884bb/Eng_Roche_oct_2024.pdf?utm_source=VBB+Insights+Mailing+List&utm_campaign=8652839a69-EMAIL_CAMPAIGN_2022_06_14_12_48_COPY_01&utm_medium=email&utm_term=0_eab2e3333c-8652839a69-450616270.

[192] Decision No. 13-D-21, relative à des pratiques mises en œuvre sur le marché français de la buprénorphine haut dosage commercialisée en ville, 18 December 2013.

This strategy was implemented primarily through two different measures. Firstly, the disparagement of generic versions by disseminating an alarmist message to doctors and pharmacists on the risks of prescribing the generic product and suggesting a change of treatment could cause psychiatric instability in patients. Secondly, pharmacists were given significant financial incentives through rebates to purchase large quantities of Subutex® with the intention of flooding the market and ensuring that the pharmacists did not have any space available to stock the generic version. The French competition authority found that there could be no objective justification for these rebates that also exceeded the maximum legal cap.

These strategies were found to be very successful and affected competition at two key stages of generic substitution. The campaign to disparage generic companies resulted in a significant increase in non-substitutable prescriptions and the discounted price levels incentivized pharmacists not to substitute Subtex® when an open prescription was written. This meant that substitution was minimal and generic competition negated.[193]

3.2.3. South Africa

Pricing strategies, such as predatory pricing, takes place in South Africa. This evergreening strategy was used by an originator company in the context of its medicinal product Herceptin® (trastuzumab).

Herceptin® (trastuzumab)

In June 2017, the Competition Commission of South Africa initiated two investigations for abuse of dominance in relation to IP-protected oncology medicinal products. While the investigation remains ongoing, allegations include patent strategies as a way to delay or prevent entry of generic alternatives of breast cancer medicinal products in South Africa.[194]

The Competition Commission of South Africa is scrutinizing whether these patenting strategies were used to engage in excessive pricing, exclusionary conduct and price discrimination with regard to the sale and supply of trastuzumab (medicinal products to treat breast and gastric cancer). A final decision of the Competition Commission of South Africa is pending.

[193] Autorité de la concurrence Medicinal Products (Press Release 19 December 2013) (https://www.autoritedelaconcurrence.fr/en/communiques-de-presse/19-december-2013-medicinal-products).
[194] 2020 WTO-WIPO-WHO Trilateral Study "Promoting Access to Medical Technologies and Innovation", p. 271.

3.2.4. Uruguay

Pricing strategies, such as predatory pricing, takes place in Uruguay. This evergreening strategy was used by the originator company in the context of MabThera® (rituximab).

MabThera® (rituximab)

The originator company marketed a package of seven medicinal products to the National Health Fund of Uruguay at a single price and additional deliveries at no cost, including Mabthera®. This practice prevented the entry of the biosimilar product into the market despite its lower cost.

The competition authority condemned the originator company to pay a fine of 814,496 USD for abusing its dominant position in the commercialisation of Mabthera®, considering its practice as a case of tying sales[195].

[195] Comisión de Promoción y Defensa de la Competencia de Uruguay, 7/12/2021, "Asunto N° 43/2019: Urufarma S.A. c/ Laboratorios Roche S.A. y/o Roche International Ltd – Denuncia".

Regulatory and non-patent issues

Denigration of generic and biosimilar products

3.3. Denigration of generic and biosimilar products

Denigration of generic and biosimilar products is the false or misleading criticism of a competitor's medicinal product in order to influence the purchasing patterns or habits of consumers. For instance, false or misleading criticism from the patent holder to prescribers about the equivalence or efficacy of a generic or biosimilar product may have the effect of limiting the impact of the market entry of generic or biosimilar products or excluding those generic and biosimilar companies from the market.

In the pharmaceutical market, misleading information may have a particularly detrimental impact, as "*given the characteristics of the medicinal products market, it is likely that the dissemination of such information will encourage doctors to refrain from prescribing that product, thus resulting in the expected reduction in demand for that type of use*".[196]

3.3.1. Argentina

The denigration of generic and biosimilar products by an originator company has clearly been identified in Argentina in the context MabThera® (rituximab). The impact of this evergreening strategy on the Argentina healthcare budgets is significant.

MabThera® (rituximab)

In a case that combines elements of sham litigation (see Section 1.5) and denigration of biosimilar products in Argentina, the originator company requested a preliminary injunction to suspend the marketing authorisation of a biosimilar version of rituximab.

Even though its petition was denied, during the process, the originator company presented a testimonial declaration from one of their medical representatives where he claimed that a patient had died from consuming the biosimilar product. This judicial action was complemented by disseminating specific denigrating messages and discredit within the medical community. To defend its product and reputation, Elea, the biosimilar company, initiated a criminal process, and it was demonstrated that the version alleged by the originator company's medical representative did not correspond to reality. Therefore, the medical representative was criminally prosecuted[197], but the trial never started because of the medical representative's death.

In 2020, the impact of the entry of the biosimilar version of MabThera®'s in Argentina was estimated to result in annual savings of approximately USD 4.4 million, potentially reaching USD 7.8 million in savings in the case of complete substitution[198]. Attempts to limit the entry of the biosimilar and/or hinder its growth can be explained by this significant impact.

[196] European Court of Justice decision in Case C-179/16, para 93. Available here.
[197] Cámara Nacional de Apelaciones en lo Contencioso Administrativo Federal, Sala II, 8/7/2015, "Productos Roche S.A.Q.e I. c/ ANMAT s/ Medida Cautelar (Autónoma)", causa 70560/2014.
[198] Jorgensen N., Spitzer E., Macadam P., Denamiel JP., Hnatiw S., Torres R., Documento de posición: impacto económico de la introducción de productos biosimilares de Bevacizumab y Rituximab al Sistema de Salud Argentino, Buenos Aires, Centro de Evaluación de Tecnologías Sanitarias (CETSA), Universidad ISALUD, 2020.

3.3.2. European Union

Over the last decade, investigations of disparagement in the pharmaceutical industry have increased significantly in the context of the denigration of generic and biosimilar products.[199]. Several cases clearly identify the denigration of generic and biosimilar products as an evergreening strategy. This is the case, for instance, in the context of Monoferric® (ferric derisomaltose); Durogesic® (fentanyl); and Plavix® (clopidogrel).

Monoferric® (ferric derisomaltose)

The European Commission has indications that for many years, an originator company may have been disparaging Monofer® by spreading misleading information regarding its safety. The European Commission is concerned that the originator company pursued a misleading communication campaign, primarily targeting healthcare professionals, which may have unduly hindered Monofer®'s uptake in the European Union. Approximately 1.8 million patients suffering from iron deficiency are currently being treated with high-dose intravenous iron products annually in the European Union. [200]

Durogesic® (fentanyl)

In December 2017, the French Competition Authority found that an originator company had abused its dominant position and consequently delayed the arrival of the generic version of Durogesic® by: (i) repeated approaches to the French agency for medical safety of health products with the aim of convincing the agency to refuse to grant at national level the generic status to competing medicinal products, despite this status already having been obtained at European level; and (ii) implementing a major campaign of falsely disparaging the generic version and using misleading language to create doubt in the minds of healthcare professionals about the effectiveness and safety of these generic products.[201]

Influenced by the alarmist messages from the originator company the French agency for medical safety of health products initially refused to recognise the generic status of competitor medicinal products, and later granted generic status with a warning attached, recommending careful monitoring of certain patients in the event of changing between fentanyl-based medicinal products.

This strategy of denigration included various messages to hospitals, doctors and pharmacists that the generic product was not equivalent, highlighting the warning it had procured from the French agency for medical safety of health products. This included the training of 300 medical sales representatives, extensive circulation of medical newsletters direct and to the specialist press, training and telephone calls.

This combined strategy was effective. 128,000 pharmacies were found to have been influenced by this message (i.e. just over half of French pharmacies). As part of a study to consider the effects of its campaign, 83% of pharmacists asked had memorised *"the risks associated with changing between fentanyl-based medicinal products"*. 12,000 healthcare professionals had the screensaver emphasising the warning from the French agency for medical safety of health products. All of this consequently meant that penetration levels of the generic product were low.

[199] Disparagement cases are well described at p. 25 of the European Commission Report "Update on Competition Enforcement in the Pharmaceutical Sector (2018-2022)" available here.
[200] See https://ec.europa.eu/commission/presscorner/detail/sl/ip_22_3882.
[201] Autorite de la concurrence, 20 December 2017: Medicinal products (Press Release) (https://www.autoritedelaconcurrence.fr/en/communiques-de-presse/20-december-2017-medicinalproducts#:~:text=Following%20a%20referral%20by%20the,generic%20version%20of%20the%20Durogesic).

Plavix® (clopidogrel)

In May 2013, the French Competition Authority found that an originator company had implemented a strategy of denigrating the generic versions of its branded medicinal product, Plavix®, to pharmacists and doctors with the aim of limiting generic entry. It was found that the originator company implemented a global and structured communication strategy *"to emphasize the […] patent related differences, however irrelevant, for generic substitution, to deter doctors and pharmacists from the generic substitution process"* insinuating *"that these differences could lead to the health professionals' liability should medical problems arise from the use of the competitors' generics"*.[202] These alleged concerns were not followed up with regulatory action, such as alerting health officials to the claimed risk of safety or efficiency. The European Commission's press release insinuates that presumably such steps would have been taken if the originator company's claims were genuine.

The French Competition Authority found that this behaviour fell outside competition on the merits and was therefore abusive. This decision was upheld on appeal.[203]

3.3.3. India

In India, a recent case in which an originator company has attempted to influence regulatory authorities by using misleading safety information in order to delay biosimilar entry relates to Herceptin® (trastuzumab):

Herceptin® (trastuzumab)

In 2016, a biosimilar company lodged a petition with the Competition Commission of India, accusing the originator company of violating Section 4 of the Competition Act relating to the abuse of a dominant position. The biosimilar company alleged that the originator company, as a dominant player, had engaged in actions (vexatious litigation and interferences with regulatory authorities) to obstruct the entry and growth of biosimilar trastuzumab in India, thereby harming competition in the relevant market. They requested the Director General under Section 26(1) of the Act to investigate the originator company, its affiliates, group entities, distributors, and agents for alleged anti-competitive practices.

On April 21, 2017, the Competition Commission, *prima facie*, found that the originator company had indeed tried to influence regulatory authorities and healthcare professionals (including tender authorities, hospitals, doctors, etc.) by sending letters and communications denigrating the biosimilar product and raising doubt about its efficacy and safety. The Competition Commission therefore concluded that it seems *"to be a part of the bigger plan/strategy […] to eliminate competition posed by biosimilars to [the originator's] products in the relevant market*". As a result, the Competition Commission instructed the Director General to conduct a comprehensive investigation into these allegations.

[202] European Commission, France: The Autorité de la Concurrence fines Sanofi-Aventis € 40 600 000 for denigrating Generic Versions of branded Drug Plavix (Press Release) [https://ec.europa.eu/competition/ecn/brief/03_2013/fr_sanofi.pdf].
[203] Arrêt du 18 octobre 2016 de la Cour de cassation: rejet.

Interplay with regulatory procedures

Issues with reference products

4. Interplay with regulatory procedures

4.1. Issues with reference products

Generic and biosimilar companies need certain quantities of the originator companies' reference products in order to conduct the necessary studies to demonstrate the generic and biosimilar product's bioequivalence to the reference product. Originator companies in some cases prevent generic and biosimilar companies from obtaining the necessary quantities of reference products for conducting studies required for regulatory approval. Preventing generic and biosimilar companies from obtaining reference samples is used by originator companies as an evergreening strategy, and may also violate domestic competition laws.

4.1.1. Canada

Canadian Generic Pharmaceutical Association member companies have found it increasingly difficult to obtain quantities of Canadian reference products for the purpose of conducting bioequivalence studies that are necessary in order to permit generic companies to file comparative submissions seeking approval for lower-cost generic products.

Difficulty accessing Canadian reference products can lead to corresponding delays in the regulatory approval process. Delayed access to more affordable medicinal products means higher costs for drug plans and higher co-payments for patients. Drug plans have to pay high costs for older medicinal products for longer than they should, meaning they cannot reinvest those potential savings in important new therapies for patients and have more difficulty controlling expenditures. Delayed market entry also financially harms generic and biosimilar companies, and unjustly enriches originator companies.

The Canadian Generic Pharmaceutical Association asked Canada's Commissioner of Competition to investigate these concerns under Section 79 of the Competition Act on February 12, 2016, and the concerns were the subject of a formal inquiry by the Competition Bureau. In addition, the Competition Bureau now routinely becomes engaged when generic companies advise that access to a Canadian reference product has been denied by an originator company. That said, Canada's early working exception (Bolar provision) does not include a mandatory or guaranteed right to reference samples and the Canadian Generic Pharmaceutical Association continues to advocate for regulatory changes to address this oversight.

The Canadian Government recognises the issues relating to accessing samples of reference products and attempts to take concrete measures in this regard:

- On December 20, 2018, the Competition Bureau of Canada issued a news release regarding its investigation into policies and practices of three originator companies that were alleged to restrict generic companies from accessing samples of Canadian reference products.[204]
- On April 2, 2020, Canada's Commissioner of Competition announced that he had discontinued an inquiry after two months of active investigation into the conduct of an originator company after the company acted to address the Commissioner's concerns. The inquiry considered allegations that the company restricted generic

[204] See https://www.canada.ca/en/competition-bureau/news/2018/12/competition-bureau-completes-abuse-of-dominance-investigation-into-practices-of-celgene-pfizer-and-sanofi.html; https://competition-bureau.canada.ca/how-we-foster-competition/education-and-outreach/position-statements/investigation-alleged-practices-celgene-pfizer-and-sanofi.

companies from accessing samples of its reference products, preventing or delaying the entry of competing products.[205]

- On August 13, 2020, Health Canada issued a notice to clarify to originator companies that elements of the Risk Management Plans required by Health Canada, such as controlled distribution programs, are not intended to restrict access to Canadian reference products for generic companies for the purposes of conducting comparative testing.[206]
- On January 20, 2022, the Competition Bureau of Canada and Health Canada's Health Products and Food Branch issued a joint statement recognising the benefits of collaborating to support Canadian's access to safe and effective pharmaceuticals and biologics. In this regard, they highlighted the ongoing issues surrounding access to samples of reference products, as generic companies face difficulties and delays in obtaining samples of the branded medicinal products.[207]

[205] See https://competition-bureau.canada.ca/how-we-foster-competition/education-and-outreach/position-statements/competition-bureau-statement-regarding-its-inquiry-alleged-anti-competitive-conduct-otsuka.
[206] See https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/notice-clarification-drug-manufacturers-sponsors-risk-management-plans.html.
[207] See https://www.canada.ca/en/competition-bureau/news/2022/01/competition-bureau-and-health-canada-strengthen-collaboration-on-key-issues-in-the-pharmaceutical-industry.html.

Interplay with regulatory procedures

Regulatory protections

4.2. Regulatory protections

Regulatory protections usually take the form of data exclusivity and market exclusivity. During data exclusivity, while generic and biosimilar products can be developed thanks to the Bolar exemption, developers cannot refer to the data of the originator product for the approval of the generic or biosimilar product. Once the data protection expires, generic and biosimilar products can obtain marketing authorisation but have to wait for the market exclusivity to expire in order to be able to enter the market. The period of protection of regulatory exclusivities may overlap with the patent protection, but is independent from it.

While there is a wrong assumption that data and market exclusivities are mandated by Article 39.3 of the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS), as described in the 2020 WTO-WIPO-WHO Trilateral Study, requires WTO members to protect test data against unfair commercial use and disclosure, but "*the TRIPS Agreement does not provide a definition of the term "unfair commercial use", nor does it identify how to achieve this protection. As a result, opinions, as well as national practices, differ on the exact requirements of Article 39.3 of the TRIPS Agreement*".[208]

4.2.1. Argentina

Argentina does not provide exclusive rights for test data submitted to regulators as a condition for the marketing approval of medicinal products. According to TRIPS Agreement requirements, Argentina only protects such data against unfair commercial use. This protection is regulated under Law No. 24.766[209] and Decree 274/2019[210], which establish penalties for those who infringe upon them and provide various administrative and judicial enforcement measures.

On May 6, 1999, and May 30, 2000, the U.S. requested consultations with Argentina regarding certain measures on the protection of patents and test data[211] at the WTO. The U.S. considered that Argentina failed to protect against unfair commercial use of the undisclosed test or other data submitted as a requirement for maker approval of medicinal or agricultural chemical products. After several consultations, on May 31, 2002, Argentina and the U.S. notified the Dispute Settlement Body that they had agreed on all the matters the U.S. raised in its consultation requests. Both States have declared that they have reached a mutually satisfactory solution to the issues raised by the U.S.[212] This solution did not require Argentina to modify its legislation on data protection, which continues to provide protection only against unfair commercial use, but not exclusivity rights.

[208] 2020 WTO-WIPO-WHO Trilateral Study "Promoting Access to Medical Technologies and Innovation", p. 81.
[209] Law No. 24766, B.O., Dec. 30, 1996.
[210] Decree No. 274/2019, B.O., Apr. 22, 2019.
[211] Request for Consultations by the United States, Argentina - Patent Protection for Pharmaceuticals and Test Data Protection for Agricultural Chemicals, WTO Doc. WT/DS171/1 (May 10, 1999).
[212] Notification of Mutually Agreed Solution According to the Conditions set Forth in the Agreement, Argentina - Patent Protection for Pharmaceuticals and Test Data Protection for Agricultural Chemicals (WT/DS171) - Argentina - Certain Measures on the Protection of Patents and Test Data (WT/DS196), WTO. Doc., WT/DS171/3, WT/DS196/4, (Jun. 20, 2002).

Glivec® (imatinib)

In 2005, the originator company initiated four "strategic lawsuits" to declare the approval regime for similar medicinal products unconstitutional and revoke the marketing authorisations for Glivec® (imatinib) obtained by generic companies. The originator company stated that the TRIPS Agreement requires Argentina to provide exclusive data protection on medicinal products. The lawsuits were rejected in all cases.

In 2011, the first judgment was issued.[213] This rejection was subsequently ratified in the remaining processes, with decisions from the three chambers of the Federal Civil and Commercial Court and the Supreme Court of Justice of Argentina.[214]

Since then, Argentina regulatory policy on data protection has remained unchanged with a clear beneficial impact, fostering competition and allowing significant savings for consumers and the public sector. According to an economic study published in 2018, the savings could be estimated at 191.7 million USD per year.[215]

4.2.2. European Union

In the European Union, the development of a medicinal product used for rare diseases, a so-called "orphan" medicinal product, entitles the developer to obtain a ten-year market exclusivity protection for each of the orphan indications. Such protection is stronger than the regulatory protection provided for non-orphan products (i.e. eight years of data exclusivity plus two years of market exclusivity). Therefore, for a medicinal product treating rare diseases, obtaining the approval for multiple orphan indications means obtaining several layers of regulatory indication protection on the same medicinal product, making it more complicated for generic and biosimilar products to reach the market on a timely basis.

The table below, from the European Commission's Report on the evaluation of the orphan legislation (2019)[216], shows orphan medicinal products for which multiple orphan indications received protections, expiring at different points in time and obtained

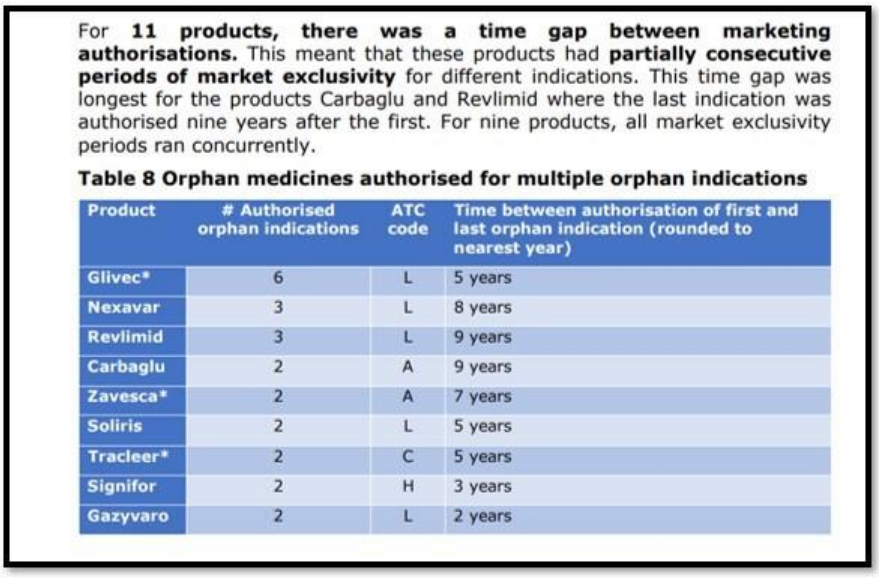
[213] Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala III, 1/2/2011, "Novartis Pharma AG c/ Monte Verde S.A. s/ varios propiedad industrial e intelectual" (n° 5619/05).

[214] Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, Sala III, 15/5/2014, "Novartis Pharma AG y otro c/ Laboratorio Varifarma S.A. y otro s/ varios propiedad industrial e intelectual" (n° 13.356/2007) and Corte Suprema de Justicia de la Nación, 7/6/2016 and 28/6/2016, "Novartis Pharma AG y otro c/ Laboratorio Varifarma S.A. y otro s/ varios propiedad industrial e intelectual" (n° 13.356/2007); Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, I, 10/11/2015, "Novartis Pharma AG c/ Laboratorio LKM S.A. s/ Varios Propiedad Industrial e Intelectual" (n° 5685/2005) and Corte Suprema de Justicia de la Nación, 30/8/2016 and 10/8/2017 "Novartis Pharma AG c/ Laboratorio LKM S.A. s/ Varios Propiedad Industrial e Intelectual" (n° 5685/2005); Cámara Nacional de Apelaciones en lo Civil y Comercial Federal, II, 18/10/2017, "Novartis Pharma AG c/ Laboratorio Dosa S.A. s/ Varios Propiedad Industrial e Intelectual" (n° 5621/2005).

[215] W. Cont, M. Panadeiros and S. Urbiztondo, 'Documento de Trabajo N° 126. Acuerdo de Comercio Mercosur - Unión Europea: Impacto sobre el gasto en medicamentos adquiridos en farmacias y por PAMI en Argentina', Fundación de Investigaciones Económicas Latinoamericanas (FIEL), January 2018, http://www.fiel.org/publicaciones/Documentos/DOC_TRAB_1517423760907.pdf accessed 17 June 2024.

[216] See https://www.politico.eu/wp-content/uploads/2020/08/final-report_orphan-regulation-study_en.pdf, p. 144.

several years after the granting of a marketing authorisation (i.e. with expiries going well beyond the expiry of the molecule's protection).



For **11 products, there was a time gap between marketing authorisations.** This meant that these products had **partially consecutive periods of market exclusivity** for different indications. This time gap was longest for the products Carbaglu and Revlimid where the last indication was authorised nine years after the first. For nine products, all market exclusivity periods ran concurrently.

Table 8 Orphan medicines authorised for multiple orphan indications

Product	# Authorised orphan indications	ATC code	Time between authorisation of first and last orphan indication (rounded to nearest year)
Glivec*	6	L	5 years
Nexavar	3	L	8 years
Revlimid	3	L	9 years
Carbaglu	2	A	9 years
Zavesca*	2	A	7 years
Soliris	2	L	5 years
Tracleer*	2	C	5 years
Signifor	2	H	3 years
Gazyvaro	2	L	2 years

A perfect example of a multi-billion orphan medicinal product where the system has been abused/misused by the originator company can be found in the context of Glivec® (imatinib).

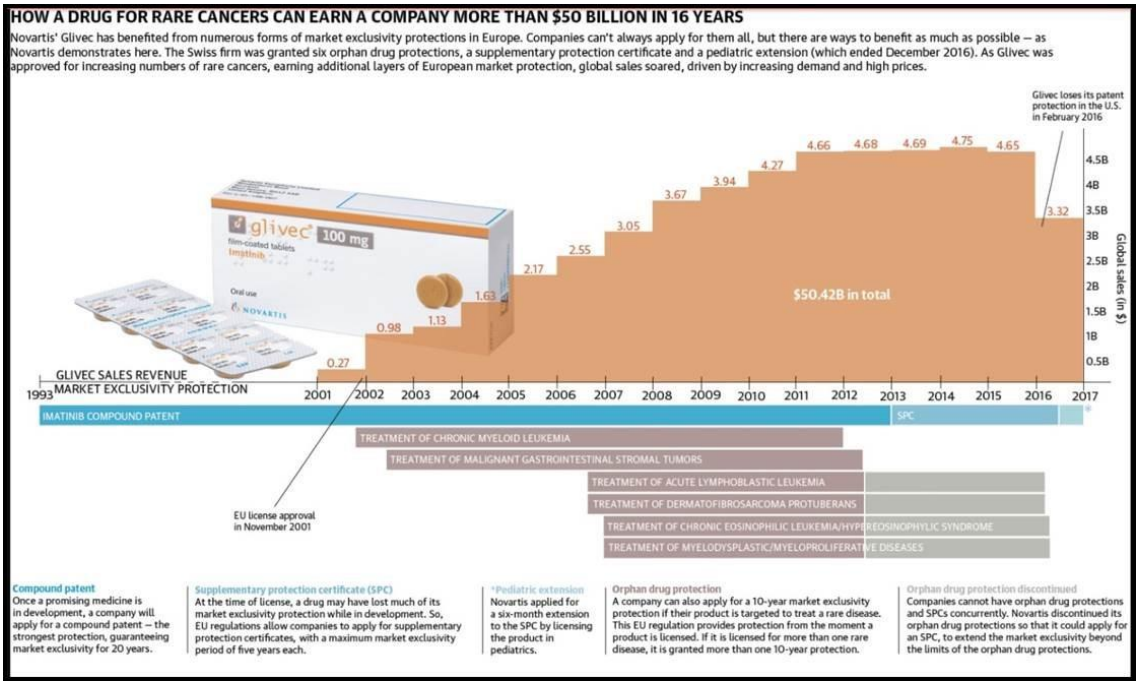
Glivec® (imatinib)

The originator company registered multiple orphan indications (and related market exclusivities) at different points in time and several years after the marketing authorisation for Glivec® (imatinib). This slide published by Politico clearly shows the multiple layers of protections[217]:

What this slide does not describe is that the originator company extended the orphan protection by conducting a paediatric study on the medicinal product that allowed it to obtain an additional six-month supplementary protection certificate protection (on the whole product, as opposed to the orphan exclusivity that covers only the paediatric indication), but only on the condition that it dropped the orphan designation. So, what occurred for Glivec® (as for almost all orphans on which a paediatric study was conducted) was that the originator company, after taking advantage of all the orphan incentives (orphan exclusivity, waiver of fees, scientific advice, etc.), renounced to the orphan designation in order to be able to get an additional, stronger protection, i.e. six months of extra supplementary protection certificate protection. The European Commission stressed that *"[t]his ability to 'switch' between protection systems can create uncertainty for developers of generic or biosimilar products that wish to reference the product as it is not clear when the protections on the product will expire."*[218]

[217] See https://www.politico.eu/wp-content/uploads/2017/10/Glivec-graphic_with-embed.png?utm_source=POLITICO.EU&utm_campaign=1989ae7551EMAIL_CAMPAIGN_2017_10_05&utm_medium=email&utm_term=0_10959edeb5-1989ae7551-189956954.

[218] See https://www.politico.eu/wp-content/uploads/2020/08/final-report_orphan-regulation-study_en.pdf, p. 277.



In addition, after obtaining several additional orphan designations, the originator company had obtained authorisation for a separate orphan medicinal product, Tasigna® (nilotinib), for the same orphan indication, which the legislation would not allow unless the holder of the existing orphan product (Glivec®) gave its consent for a similar medicinal product to be authorised; consent that the originator company gave to itself. In this way, the company extended the market exclusivity protection from ten to sixteen years, i.e. from 2011 (when the orphan exclusivity of Glivec® expired) to 2017 (year of expiry of the Tasigna®'s exclusivity). Considering that the global annual sales of Glivec® in 2015 were of 4.65 billion USD and those of Tasigna® of 1.63 billion USD, the impact of this tactic was not only on patient access but also on healthcare budgets.[219] This was a clear misuse of the system, which indeed the European Commission has proposed to remove in the current pharma legislation reform.

The Medicines Law & Policy Report on Orphan Medicinal Products in the European Union (2019) presents the case of Glivec as "*Evergreening the orphan way?*"[220]

The ECORIS Report to the Dutch Ministry of Health, 2015: *"How well does regulation work? The cases of pediatric medicines, orphan drugs and advanced therapies"* stressed that *"[t]he Orphan Regulation is sometimes used for registering low-cost magistral formulae to bring high-priced specialty drugs to the market if the costs are not justified by the registration requirements. It is also clear that due to the availability of magistral formulae there is no unmet medical need as is the case for other orphan drugs. This strategic use of the regulation should be evaluated to prevent turning well intended regulations into perverse incentives."*

[219] Pharmaceutical Technology: https://www.pharmaceutical-technology.com/features/featurethe-worlds-most-sold-cancer-drugs-in-2015-4852126/?cf-view&cf-closed.

[220] See https://medicineslawandpolicy.org/wp-content/uploads/2019/06/European-Union-Review-of-Pharma-Incentives-Orphan-Medicinal-Products.pdf, p.9.

The above elements should be considered carefully, since as shown in the slide below, orphan medicinal products are ten times more costly per patient.

Source: Profitability and Market Value of Orphan Drug Companies: A Retrospective, Propensity-Matched Case-Control Study, Dyfrig A. Hughes and Jannine Poletti-Hughes, PLoS One. 2016; 11(10): e0164681.

The evergreening strategy applied by the originator company on Glivec® resulted in a patient delay of six years, meaning that the market entry of the generic companies was delayed by six years due to the artificial interpretation of the law, allowing the originator company to extend the exclusivity by six additional years with its second product.

4.2.3. Mexico

Holders of marketing authorisations of reference products have deployed litigation strategies to obtain the protection of test data in respect of new therapeutic indications or variations to the original formulations, preventing generic or biosimilar products from being able to rely on the originator's products for rapid approval. Indeed, in Mexico, data exclusivity can be prolonged by five years every time a new indication on a medicinal product is approved.

In all the known cases, the Specialized Branch of the Administrative Affairs Federal Court has considered that the new formulations and the new therapeutic indications contained in the modifications to the conditions of the original marketing authorisation are allegedly the result of a considerable effort on the part of the holder of the marketing authorisation, since their preparation involved an economic effort, and technical and scientific factors to obtain those modifications, which, in its view, justifies classifying them as new molecules. On the basis of these rulings, the Mexican Regulatory Authority grants a five-year data exclusivity protection to each new indication or modification to the formulation, counted from the time that the Mexican Regulatory Authority authorises each of them. This makes it complicated for competing companies to obtain timely marketing authorisations of generic or biosimilar versions of the reference product, as demonstrated in the case below concerning Humira® (adalimumab).

Humira® (adalimumab)

The holder of the marketing authorisation for Humira®, which was approved in Mexico on May 15, 2003, obtained approvals for new therapeutic indications in 2014, 2016, 2018, 2019, 2021, and 2022. By doing so, it managed to extend the data exclusivity protection that was attached to the original adalimumab (i.e. 5 years

from the granting of the original marketing authorisation in 2003) from May 2008 to at least 2024, thus delaying biosimilar competition by 16 years.

Mexico soon must implement data protection in accordance with the United States-Mexico-Canada Agreement within five years after its entry into force (July 1, 2020). Thanks to the "Protocol replacing the North American Free Trade Agreement with the Agreement between the United States of America, the United Mexican States, and Canada (UMSCA Protocol)", the Mexican Regulatory Authority will have to recognise a single protection of at least five years to the Test Data exclusively to: i) new medicinal products related to chemically synthesised medicinal products, and ii) combinations of medicinal products that contain a chemical entity that has not been previously authorised in Mexico, for the same period (Article 20.48).

Conclusion

5. Conclusion

As shown in this report, evergreening strategies take multiple forms and are used by originator companies worldwide, with serious impacts on healthy and timely competition. The global dimension of these strategies is demonstrated by the fact that, in some cases, the same evergreening strategies are applied simultaneously across multiple jurisdictions, while in other cases multiple strategies are used in combination in the same jurisdiction (e.g. patent thickets in combination with patent linkage). The coexistence of the two fundamental healthcare objectives, "innovation" and "access", is constantly disrupted by evergreening practices.

These findings highlight the urgent need for reinforcing the balance in the intellectual property and regulatory systems to address the evergreening strategies employed by some originator companies. These strategies, which unduly extend monopolies and delay the market entry of generic and biosimilar products, significantly hinder patient access to affordable treatments. To ensure timely and equitable access to essential medicinal products, it is imperative to amend existing laws, regulations, and practices that enable such tactics by adopting a more holistic approach. In fact, the strategies described in this report are frequently made possible by the fact that regulatory, intellectual property and market access rules are often designed without necessarily taking into account their possible interplay, and thereby, allowing their (mis)use by dominant companies. Reforms should include an increasingly higher role for competition authorities, which should not only enforce national competition rules but also get actively involved in shaping policies and guaranteeing the right systemic safeguards. This will help promote a more competitive pharmaceutical market and improve healthcare outcomes globally.

This report provides sufficient cases and examples of strategies employed to extend monopoly and stifle competition, providing guidance for patent offices, health authorities and competition agencies to prevent the granting of ineligible patents, exclusionary practices or regulatory procedures that harm competition and ultimately affect healthcare systems and patients. Competition and health authorities should establish formal international coordination to prevent patent systems from being misused or abused, distorting competition and delaying access to generic and biosimilar products. In addition, it is crucial that patent offices and competition agencies are robust and well equipped. Robust institutions play a dual purpose: patent offices grant quality patents, minimising the risk of invalidation, while competition agencies strategically intervene in markets, avoiding both false positives (unnecessary intervention) and false negatives (missed opportunities).

A balanced intellectual property system is crucial for fostering both innovation and patient access. In this regard, the International Generic and Biosimilar Medicines Association (IGBA) remains committed to engaging with key stakeholders globally, regionally and locally to advocate for and propose specific pro-competitive policies that effectively address these challenges.

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