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EUROPEAN PHARMACEUTICAL PATENT CHALLENGES: A CASE-BASED PERSPECTIVE

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Abstract

Pharmaceutical patents play a central role in innovation-driven drug development by granting time-limited protection intended to reward research investment. However, although substantive patent law is formally harmonized under the European Patent Convention (EPC), enforcement remains nationally fragmented. Divergent judicial interpretations can influence legal certainty, pharmaceutical market dynamics, generic entry timing, and healthcare expenditure. This study examines how variation in national patent adjudication affects innovation incentives, competition, and public health outcomes in Europe. Using three case studies - rivaroxaban, apixaban, and tadalafil - the analysis integrates legal doctrine with pharmaceutical market data to assess how interpretations of inventive step, plausibility, and sufficiency of disclosure influence the timing of generic entry. The findings indicate that judicial fragmentation leads to asynchronous generic entry across member states, resulting in uneven price convergence and differences in healthcare expenditure. The establishment of the Unified Patent Court (UPC) may improve legal consistency, although its long-term impact on pharmaceutical market dynamics remains to be fully evaluated.

Rezumat

Brevetele farmaceutice sunt deosebit de importante pentru inovațiile în domeniul dezvoltării medicamentelor, oferind o protecție limitată în timp, menită să recompenseze investițiile în cercetare și dezvoltare. Cu toate acestea, deși normele materiale privind brevetarea sunt armonizate la nivel european prin intermediul Convenției privind Brevetul European (EPC), aplicarea și punerea lor în executare rămân fragmentate la nivel național. Diferențele de interpretare juridică pot influența securitatea, dinamica pieței farmaceutice, momentul intrării pe piață a medicamentelor generice și nivelul cheltuielilor din sistemele de sănătate. Acest studiu analizează modul în care variațiile în soluționarea litigiilor privind brevetele la nivel național influențează stimulentele pentru inovare, concurența și rezultatele în domeniul sănătății publice în Europa. Pe baza a trei studii de caz, rivaroxaban, apixaban și tadalafil, această analiză integrează doctrina juridică și datele privind piața farmaceutică pentru a evalua modul în care interpretarea criteriilor de activitate inventivă, plauzibilitate și suficiență a descrierii influențează momentul introducerii medicamentelor generice pe piață. Fragmentarea jurisprudențială determină o intrare asincronă a medicamentelor generice în diferite state membre, ceea ce conduce la convergențe inegale ale prețurilor și la diferențe semnificative în cheltuielile pentru sănătate.

Keywords: pharmaceutical patents, generic medicines, intellectual property, market access, Unified Patent Court

Introduction

Pharmaceutical innovation relies on a delicate balance between scientific discovery, market exclusivity, and equitable patient access. The patent system is central to this balance, providing time-limited monopoly rights that enable companies to recover the immense costs of research and development (R&D) while incentivizing continued innovation. Bringing a new molecular entity (NME) to market typically requires 10 - 15 years of research and often exceeds 1 billion euros in investment (1, 2). During this period, effective intellectual property (IP) protection remains the primary mechanism for securing returns and sustaining the pipeline of innovative therapies (3).

Within the European Union, pharmaceutical patents operate at the intersection of science, law, and public health. Although the European Patent Convention (EPC) provides a harmonized system for patent examination, post-grant enforcement remains fragmented across national jurisdictions (4). Each granted European patent becomes a bundle of national rights, adjudicated under domestic procedural rules. As a result, identical patents have been simultaneously upheld and invalidated in different countries (5). This situation introduces uncertainty for originators, generics, regulators, and healthcare providers, with direct consequences for the timing of market entry and medicine affordability.

In the pharmaceutical sector, exclusivity extends well beyond the standard 20-year patent term. Under the data and market exclusivity regime established by Directive 2001/83/EC as amended by Directive

2004/27/EC (6), medicinal products authorized in the EU, including *via* the centralized procedure under Regulation (EC)726/2004 (7), benefit from the "8+2(+1)" model. This prevents generic manufacturers from relying on the originator's preclinical and clinical data for 8 years and prohibits market entry for a further 2 years, with a possible 1-year extension granted for approval of a significant new therapeutic indication. In addition, Supplementary Protection Certificates (SPCs) may prolong patent protection by up to five years to compensate for time lost during the regulatory approval process conducted by the European Medicines Agency (EMA) (8). Moreover, Regulation (EC) No 1901/2006 (9) on medicinal products for paediatric use provides an additional 6 month extension of the SPC or patent term upon successful completion of an agreed Paediatric Investigation Plan (PIP). When combined, these legal and regulatory protections can maintain monopoly conditions for more than 25 years after initial patent filing date.

While such protection sustains innovation, it can also delay competition and strain healthcare budgets. For instance, the immediate entry of generic atorvastatin in the United Kingdom (UK) in 2012 triggered a price drop of over 85%, saving the National Health Service (NHS) an estimated £350 million in the first year alone (10). Conversely, extended litigation or conflicting national rulings can defer generic market access, prolonging high prices for essential medicines such as anticoagulants and oncology therapies. From a pharmaceutical perspective, the implications extend well beyond legal doctrine. Fragmented adjudication generates unequal patient access within the EU single market, distorts competition among generic manufacturers, and undermines evidence-based pricing mechanisms. Furthermore, regulatory bodies such as the EMA and national Health Technology Assessment (HTA) agencies depend on patent clarity to plan market authorization, tendering, and reimbursement pathways (11, 12).

The following three case studies: rivaroxaban (Bayer), apixaban (Bristol Myers Squibb), and tadalafil (ICOS/ Eli Lilly), illustrate the pharmaceutical significance of these divergences. All three involve small-molecule drugs with blockbuster sales and major clinical indications (thrombosis prevention and erectile dysfunction). Each demonstrates how divergent national interpretation of inventive step, plausibility, and sufficiency of disclosure can alter the commercial and therapeutic landscape across Europe.

The objective of this paper is therefore twofold: to examine how divergent judicial reasoning across European courts influences pharmaceutical innovation, market competition, and access to medicines, and to assess how the emerging Unified Patent Court (UPC) framework may foster a more harmonized and health-oriented patent environment that supports both innovation and patient affordability. By integrating legal analysis with pharmaceutical, regulatory, and market perspectives, the paper aims to contribute to a multidisciplinary understanding of patent harmonization as a determinant of public health outcomes and industrial competitiveness.

The European Patent Framework

Structure and function of the EPC system

Under the EPC, applicants may file a single European patent application designating multiple member states. Once granted by the European Patent Organization (EPO), the "bundle patent" requires national validation within three months, involving translation obligations and payment of national fees. Each validated patent then becomes an independent national right, enforceable or revocable before domestic courts (13, 14).

While the EPO provides an opposition procedure enabling third parties to challenge a patent's validity within nine months of grant (EPC Art. 99 - 105), litigation thereafter transfers to national jurisdictions (13). Because each court applies its domestic rules of evidence, procedure, and expert testimony, outcomes may diverge even where the underlying prior art is identical. Studies show that fewer than 30% of parallel European patent cases reach congruent results across all jurisdictions. This inconsistency is particularly pronounced between major European markets. For example, litigation outcomes coincide in only 28.6% of cases adjudicated in both Germany and the United Kingdom, and in just 22.7% of cases litigated in Germany and the Netherlands (5).

Layered pharmaceutical exclusivities and market dynamics

The cumulative protection from data and market exclusivity, as well as SPC and pediatric extension creates a complex time-based landscape in the field of pharmaceutical patents in which patent expiry does not necessarily coincide with market entry of generics. Consequently, litigation over secondary patents, such as those covering polymorphs, dosage regimens or formulations, has become a strategic tool for prolonging exclusivity; a practice commonly referred to as "evergreening". Courts' different attitudes toward these secondary claims have produced pronounced jurisdictional variability (15-18).

Legal standards for patentability

The EPO defines three core substantive requirements: novelty (Art. 54), inventive step (Art. 56), and industrial applicability (Art. 57) (13). Among these, inventive step is the most argumentative in litigation. The EPO applies the "problem-solution approach", asking whether a skilled person, having regard to the prior art, would have been motivated to reach the claimed invention with a reasonable expectation of success (19). National courts, how-

ever, interpret "reasonable expectation" differently. Anglo-Saxon jurisdictions emphasize predictability of success, while continental systems often require a demonstrable "technical effect" beyond what was obvious to the skilled person (20, 21). This divergence in interpretation contributes directly to the high rate of post-grant challenges within the pharmaceutical sector. It shows that questions of inventive step and plausibility are not merely legal abstractions, but practical determinants of market exclusivity, regulatory timing, generic entry, and the moment at which patients can realistically gain access to affordable medicines. This combined doctrinal and empirical context therefore provides the analytical foundation for the comparative case studies that follow.

Comparative Case Studies

Rivaroxaban (Xarelto®, Bayer)

Background. Rivaroxaban, a direct Factor Xa inhibitor, was developed by Bayer AG and approved in 2008 for prevention of thromboembolic disorders (22). Its blockbuster status, generating over € 4 billion annually (23), made the compound central to a series of litigations across Europe. Patent EP 1845961, filed in 2006 (priority 2005), protected the use of rivaroxaban in a once-daily, immediate-release oral dosing form administered for at least five consecutive days for treatment of thromboembolic disorders (24).

Opposition before the EPO. Multiple generics (including Sandoz, Actavis and Teva) opposed the patent (25), arguing lack of inventive step over three scientific posters by Harder and Kubitza that disclosed pharmacokinetic properties of the molecule (26-28). The EPO's Opposition Division initially revoked the patent, but the decision was set aside by the Boards of Appeal in 2021, resulting in maintaining the claims (29).

United Kingdom (UK). In Sandoz AG & Ors versus Bayer AG ([2024] EWHC 796 (Pat)), the Patents Court held that the claimed once-daily dosing regimen lacked inventive step. Applying the UK approach to obviousness, the court considered whether the prior-art posters (26-28), when read together, would motivate a skilled pharmacologist to conduct Phase II trials with a once-daily schedule. The court concluded that the data on half-life and tolerability made this an obvious next step, rendering the patent invalid (30). The decision was upheld by the Court of Appeal later that year.

France (FR). In Sandoz versus Bayer (Paris TJ, RG 22/08612, 2024), the court reached a parallel conclusion, emphasizing that optimizing a dosage frequency through routine clinical trials does not satisfy inventive step under Art. 56 EPC. The court further highlighted the public health impact: delaying generic rivaroxaban would cost the French Health Insurance Fund over €180 million annually (31).

Netherlands (NL). Conversely, the District Court of The Hague (C/09/637811/HA ZA 22-934, 2023) upheld the patent. The court reasoned that a skilled person could not reasonably expect a once-a-day regimen to maintain anticoagulant efficacy given rivaroxaban's reported half-life of 4 - 6 hours (27, 28). It emphasized the distinction between a mere possibility of success and reasonable expectation of success, applying the higher evidentiary threshold traditionally required under the Dutch law (32, 33).

Germany (DE). In 2024 the Regional Court of Munich granted Bayer a preliminary injunction against Sandoz and Stada, barring market entry (Case 6 U 2277/24) (34). Yet in July 2025 the Federal Patent Court revoked the patent (3 Ni 11/22), finding that Bayer's own clinical disclosures undermined its claim to non-obviousness (35).

Rivaroxaban illustrates how identical evidence, Harder and Kubitza's data, were interpreted variously. Patients in the UK and France gained early access to generics, while those in the Netherlands and Germany faced continued monopoly pricing until 2026.

Apixaban (Eliquis®, Bristol Myers Squibb)

Background. Apixaban, another Factor Xa inhibitor, was jointly developed by Bristol Myers Squibb (BMS) and Pfizer. Patent EP 1427415 B1 covered the compound's use and synthesis pathway, with SPCs extending protection in most EU states to 2026 (36). Given its structural similarity to rivaroxaban, apixaban became the focus of parallel validity challenges by several generics.

United Kingdom (UK). In Sandoz Ltd & Teva Pharmaceutical Industries Ltd versus Bristol Myers Squibb Holdings Ltd ([2022] EWHC 822 (Pat)), the Patents Court revoked EP 1427415 for insufficiency of disclosure. The court held that the specification did not plausibly demonstrate the compound's inhibitory activity against Factor Xa, rendering the technical effect speculative. Without such plausibility, the claim failed under Art. 83 EPC. The decision was affirmed on appeal (37).

Continental Europe. In contrast, courts in France, Spain, and the Netherlands considered the disclosure sufficient. The Commercial Court of Barcelona in 2024 overturned its earlier revocation, holding that the description of biochemical assays was adequate and that plausibility requirements should not be equated with full experimental proof (38). Similarly, the District Court of The Hague (C/09/643554/HA ZA 23-199, 2024) rejected Sandoz's challenge, emphasizing that the EPC does not mandate submission of clinical data for patentability (39, 40).

Switzerland (CH). The Swiss Federal Patent Court (O2022_007, 2024) and the Federal Supreme Court (4A_233/2024) likewise upheld validity, treating minor

errors in priority declaration as formal defects without substantive impact (41, 42).

The apixaban litigation demonstrates the uncertainty surrounding the "plausibility standard" for pharmaceutical inventions. While UK courts demanded a robust experimental basis, continental courts accepted broader interpretations of Art. 83 EPC (13). The result was a patchwork of protection across Europe despite identical scientific evidence.

Tadalafil (Cialis®, ICOS/Eli Lilly)

Background. Patent EP 1173181, owned by ICOS Corporation and licensed to Eli Lilly, claimed a low-dose (1 - 5 mg) regimen of tadalafil for daily administration in erectile dysfunction. Earlier patents had covered the compound and its on-demand use; the new claim focused on chronic therapy with reduced side effects. The case became a touchstone for assessing whether dose-optimization constitutes an inventive step (43).

United Kingdom (UK). In Actavis Group PTC EHF versus ICOS Corporation ([2019] UKSC 15), the Supreme Court affirmed revocation, holding that the 5 mg dose was an obvious result of routine clinical testing. It was clarified that "a dose-finding study is an obvious task for the skilled team once a compound's therapeutic potential is known". The court rejected the argument that reduced side effects constituted an unexpected technical effect, as such effects were discoverable through ordinary trials (44).

Germany and Netherlands (DE and NL). German and Dutch courts mirrored the UK's reasoning (3 Ni 22/15 (EP); 3 Ni 27/15 (EP) and BGH X ZR 65/18; Rechtbank Den Haag C/09/532013/HA ZA 17-488), emphasizing that Art. 56 EPC does not protect discoveries made by routine optimization of known compounds. Both decisions revoked the patent in their jurisdictions (45, 46).

Denmark and Finland (DK and FI). By contrast, the Danish High Court (A-49-17) and the Finnish Market Court (MAO 131/19) maintained the patent, finding that identifying a safe daily dose for chronic administration involved a non-obvious technical consideration given the risk of cumulative exposure. They considered the claimed invention a "new therapeutic application" rather than mere dose optimization (47, 48).

The tadalafil dispute underscores how courts differentiate between routine experimentation and true invention. The lack of consensus on the inventive threshold for dosage regimens reveals a fundamental doctrinal division within Europe's patent legal interpretation.

Legal determinants of post-exclusivity market outcomes

The comparative overview presented in Table I highlights how differences in pharmacological profile, market size, and legal protection mechanisms translate into structurally distinct post-exclusivity market trajectories. Rivaroxaban and apixaban, two high-turnover anticoagulants with long-term use across large patient populations, represent the highest financial stakes. In such therapeutic areas, even a single year of delayed generic entry corresponds to hundreds of millions of euros in additional public health expenditure.

Table I

Comparative pharmaceutical and market overview of rivaroxaban, apixaban, and tadalafil

Drug (INN)	ATC Code	Mechanism of action	Major indications	EMA approval Year	Global sales ($B, peak)	Year of first generic entry	Price reduction in the UK after generic entry under reimbursement schemes (%)
Rivaroxaban	B01AF01	Direct Factor Xa inhibitor	AF, DVT, PE prevention	2008	5.7 (2017) (49)	2024 (UK)/ 2026 (DE, NL)	65 - 85% (53)
Apixaban	B01AF02	Selective Factor Xa inhibitor	AF, DVT, PE prophylaxis	2011	20.7 (2024) (50, 51)	2022 (UK)/ 2025 (NL)	> 80% (54)
Tadalafil	G04BE08	PDE5 inhibitor	ED, BPH, PAH	2002	2.2 (2017) (52)	2017 (2.5 mg protected longer - 2019) (UK)/2021 (FI, DK)	30 - 95% (only the 2.5 mg strength showed around 30% reduction, whereas other strengths showed around 90% price reduction) (55, 56)

AF – Atrial fibrillation; DVT – Deep vein thrombosis; PE – Pulmonary embolism; ED – Erectile dysfunction; BPH – Benign prostatic hyperplasia; PAH – Pulmonary arterial hypertension

The combined pharmaceutical and legal analysis reveals a clear interdependence between therapeutic innovation and patent decision. In each case, courts applied differing interpretations of inventive step and plausibility, directly shaping market access dynamics. Early revocation or tolerant enforcement accelerated generic competition, yielding significant price reductions and improved affordability. Conversely, extended exclusivity due to sustained patent protection preserved high originator revenues but delayed equitable access.

From a policy viewpoint, these findings underscore that legal harmonization is not only a matter of legal interpretation but a determinant of pharmaceutical availability, cost-effectiveness, and public health equity across Europe.

Discussion

Fragmentation and its pharmaceutical consequences

The case analyses of rivaroxaban, apixaban, and tadalafil demonstrate that Europe's fragmented litigation framework does not only create legal inconsistency, but it also produces noticeable pharmaceutical consequences. When identical patents are upheld in one jurisdiction and revoked in another, the timing of generic entry and market competition differ by years, directly affecting drug affordability. For rivaroxaban, generics entered the UK and French markets in 2024 following invalidation but will remain excluded in the Netherlands and Germany until 2026. During this two-year interval, Germany's statutory health insurance funds (Gesetzliche Krankenversicherung, GKV) and patients are expected to face more than €700 million in additional cumulative costs, assuming a post-generic price reduction of only 50% (57).

Such delays impede the EU's policy objective of equitable access to medicines, protected in the Pharmaceutical Strategy for Europe (58). The fragmentation also disincentivizes generic manufacturers, who must invest in parallel litigation and face uncertainty over launch timing. In high-turnover therapeutic classes, each additional month of exclusivity can yield tens of millions of euros for the originator company but equally burdens healthcare budgets and patients.

Interaction of patent and regulatory exclusivity

The pharmaceutical lifecycle illustrates that exclusivity is multi-layered. Even after patent revocation, data and market exclusivity can sustain effective monopoly for several years. When litigation outcomes diverge, national regulators face uncertainty: should marketing authorization be granted if a parallel patent remains valid elsewhere? The absence of a uniform legal outcome complicates EMA coordination and undermines the principle of a single regulatory market.

From a scientific standpoint, dose-optimization patents such as tadalafil's low-dose claim reflect routine clinical experimentation rather than radical innovation. Yet the legal protection of such "secondary patents" effectively extends exclusivity without additional therapeutic benefit, a practice often termed "evergreening". For healthcare policymakers, distinguishing genuine incremental innovation from patent driven monopoly becomes critical to ensure rational resource allocation.

Innovation incentives vs. public health

A persistent dilemma in pharmaceutical policy lies in reconciling innovative incentives with patient affordability. Strong patent protection fosters R&D investment, particularly in high-risk areas such as rare diseases and biologics (59). However, when protection becomes excessive or unpredictable, it undermines public trust and slows adoption of cost-saving generics and biosimilars.

Empirical studies indicate that average generic penetration within one year after patent expiry ranges from 50% to 70% across EU countries, resulting in price reductions of 40% to 80% (60). Where litigation delays entry, this price erosion is postponed, leading to cumulative losses exceeding several billion euros across European healthcare systems. These findings highlight that patent fragmentation transcends legal boundaries, representing a pharmaceutical-economic barrier to efficient and equitable healthcare delivery.

Policy and research implications

The European Commission's ongoing revision of pharmaceutical legislation (expected in 2026) presents an opportunity to link intellectual property harmonization with broader regulatory reform. Establishing an integrated data infrastructure connecting patent status, regulatory approvals, and pricing data could enhance market transparency and reduce delays associated with fragmented post-exclusivity transitions.

To illustrate how doctrinal variation translates into systemic consequences, Table II summarizes the structural relationship between key legal issues and their pharmaceutical and policy implications.

Table II

EPC fragmentation: legal issues, pharmaceutical consequences, and policy implications

Legal Issue	Pharmaceutical Consequence	Policy Relevance
Divergent national judgments	Asynchronous generic entry; unequal patient access	Contradicts EU single-market and health-equity principles
Broad interpretation of inventive step	Extended exclusivity for marginal improvements	Escalates medicine expenditure
Lack of harmonized plausibility standard	Uncertain R&D predictability	Discourages balanced innovation planning
Fragmented litigation	High transaction costs for generics	Discourages competition, increases payer burden

Harmonization pathways: the role of the unified patent court

The UPC, operational since June 2023, represents a transformative step toward harmonizing patent adjudication across Europe (61). For the pharmaceutical sector, where litigation outcomes directly shape market dynamics and patient access, the UPC provides an unprecedented opportunity to unify the interpretation of inventive step, plausibility, and sufficiency of disclosure within a single judicial framework (62, 63).

The establishment of the UPC is expected to yield several advantages for the pharmaceutical industry. Table III summarizes its three principal benefits: predictability, efficiency, and transparency, and their relevance to pharmaceutical regulation and market access.

Table III

Key benefits of the unified patent court system and their pharmaceutical relevance

Benefit	Description	Pharmaceutical Relevance
Predictability	A single, uniform judgment applicable across member states enables consistent outcomes and more accurate forecasting of market entry dates and pricing negotiations.	Facilitates coordinated regulatory planning, tendering, and reimbursement decisions.
Efficiency	Consolidated litigation processes reduce duplication of national cases and shorten dispute resolution timelines.	Lowers legal costs for innovators and generics, expediting patient access to affordable medicines.
Transparency	A centralized database of UPC decisions improves visibility of patent status and litigation outcomes across Europe.	Enhances data sharing among regulators, payers, and manufacturers, strengthening evidence-based policy and market oversight.

For innovators, the UPC is expected to enhance confidence in IP protection and attract greater investment in high-risk therapeutic areas such as oncology and rare diseases. For healthcare systems, consistent rulings should mitigate the costly fragmentation that delays price competition and equitable access to essential medicines. Unified enforcement also enables closer integration between EPO patent data, EMA regulatory decisions, and HTA outcomes, linkages that could make patent, pricing, and reimbursement decisions more coherent across the EU.

However, the system's success will depend on broad engagement from the pharmaceutical sector. During the transitional period (2023 - 2030) (64), many companies may prefer to maintain proceedings before national courts to minimize the risk of EU-wide patent revocation. Over time, as case law develops and procedural expertise increases, confidence in the new system is expected to grow. Ensuring the active involvement of pharmaceutical specialists within the UPC's judicial panels and fostering structured collaboration with regulatory and HTA bodies will be crucial to achieving both legal and scientific robustness.

Looking ahead, the UPC has the potential to serve as the foundation of a more integrated European pharmaceutical innovation ecosystem, one that aligns legal certainty with public health objectives. Its long-term success will hinge on maintaining a balance between strong IP incentives and transparent, predictable, and equitable pathways for market competition and patient access.

Conclusions

Patent protection remains essential for sustaining pharmaceutical innovation, yet it must operate within a framework that also ensures timely access to affordable medicines. The comparative analysis of rivaroxaban, apixaban, and tadalafil shows that divergent judicial interpretations across European jurisdictions can disrupt the balance between innovation and public welfare. Differences in national patent adjudication, particularly in assessing inventive step, plausibility, and sufficiency of disclosure lead to asynchronous generic entry and uneven market competition among member states. This fragmentation undermines legal certainty for both innovators and generic manufacturers and contributes to disparities in patient access and healthcare expenditure.

The establishment of the UPC represents a significant institutional reform with the potential to mitigate these inconsistencies through centralized litigation and more uniform interpretation of pharmaceutical patents. A coherent UPC jurisprudence could reduce litigation complexity, accelerate dispute resolution, and improve predictability for market entry.

However, legal harmonization alone is insufficient. Effective pharmaceutical governance requires stronger coordination among patent authorities, regulatory agencies, and HTA bodies. Integrating patent transparency with regulatory and clinical evidence would support more informed decisions while promoting both innovation and equitable patient access to medicines.

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AI use disclosure

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Conflict of interest

The authors declare no conflict of interest.

References

1. Chatterjee B, Steiner R, Kaul G. Industry perspective – what does industry need to accelerate drug product and process development? Pharm Res. 2024;41:7-11.
2. Schlander M, Hernandez-Villafuerte K, Cheng CY, Mestre-Ferrandiz J, Baumann M. How much does it cost to research and develop a new drug? A systematic review and assessment. Pharmacoeconomics. 2021;39:1243-1269.
3. Williams HL. How do patents affect research investments? Annu Rev Econom. 2017;9:441-469.
4. Zingg R, Elsner E. Protection heterogeneity in a harmonized European patent system. Eur J Law Econ. 2020;50:87-131.
5. Cremers K, Ernicke M, Gaessler F, Harhoff D, Helmers C, McDonagh L, et al. Patent litigation in Europe. Eur J Law Econ. 2017;44:1-44.
6. European Parliament and Council. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use. Off J Eur Union. 2004;L136:34-57.
7. European Parliament and Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Off J Eur Union. 2004;L136:1-33.
8. European Parliament and Council. Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products. Off J Eur Union. 2009;L152:1-10.
9. European Parliament and Council. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Off J Eur Union. 2006;L378:1-19.
10. Generics and Biosimilars Initiative (GaBI). Lipitor generics saved UK NHS £350 million in first 12 months [online]. GaBI; 2013 [cited 2025 Dec 22]. Available from: https://gabionline.net/generics/general/Lipitor-generics-saved-UK-NHS-350-million-in-first-12-months.
11. Vondeling GT, Cao Q, Postma MJ, Rozenbaum MH. The impact of patent expiry on drug prices: a systematic literature review. Appl Health Econ Health Policy. 2018;16:653-660.
12. Panteli D, Arickx F, Cleemput I, Dedet G, Eckhardt H, Fogarty E, et al. Pharmaceutical regulation in 15 European countries: a review. Health Syst Transit. 2016;18(5):1-122.
13. European Patent Office. Convention on the Grant of European Patents (European Patent Convention) [online]. 17th ed. Munich: European Patent Office; 2020 [cited 2025 Dec 25]. Available from: https://www.epo.org/law-practice/legal-texts/epc.html.
14. European Patent Office. European Patent Guide – Validation procedures (How to get a European patent) [online]. Munich: European Patent Office; 2023 [cited 2025 Dec 25]. Available from: https://link.epo.org/web/legal/guide-epc/en-how-to-get-a-european-patent-2023.pdf.
15. Kapczynski A, Park C, Sampat BN. Polymorphs and prodrugs and salts (oh my!): an empirical analysis of "secondary" pharmaceutical patents. PLoS One. 2012;7(12):e49470.
16. Kanavos P, Costa-Font J, Seeley E. Competition in off-patent drug markets: issues, regulation and evidence. Econ Policy. 2008;23(55):500-544.
17. Grabowski H, Brain C, Taub A, Guha R. Pharmaceutical patent challenges: company strategies and litigation outcomes. Am J Health Econ. 2017;3(1):33-59.
18. Organisation for Economic Co-operation and Development (OECD). Competition and generic pharmaceuticals [online]. In: OECD Roundtables on Competition Policy Papers No. 170. Paris: OECD Publishing; 2015 [cited 2025 Dec 26]. Available from: https://doi.org/10.1787/380496a7-en.
19. European Patent Office. Guidelines for Examination in the European Patent Office (April 2025) [online]. Munich: European Patent Office; 2025 [cited 2025 Dec 27]. Available from: https://www.epo.org/en/legal/guidelines-epc/2025/g.html.
20. England P. Patents and plausibility. J Intellect Prop Law Pract. 2014;9(1):22-30.
21. Li X, Dai L, Ouyang S, Zhu N. A comparative analysis of the inventive step standard in the EPO, SIPO and USPTO. J Intellect Prop Law Pract. 2013;8(7):539-545.
22. Solomon C, Niță DT, Ozon EA, Fița AC, Viziteu HM, Musuc AM, et al. An overview of the pharmaceutical profile of rivaroxaban. Farmacia. 2025;73(1):1-8.
23. Reuters. Bayer's patent for blood thinner Xarelto invalid, UK court rules [online]. Reuters; 2024 [cited 2025 Dec 29]. Available from: https://www.reuters.com/business/healthcare-pharmaceuticals/bayers-patent-blood-thinner-xarelto-invalid-uk-court-rules-2024-04-12/.
24. European Patent Office. EP1845961B1 - Treatment of thromboembolic disorders with rivaroxaban [online].

Munich: EPO; 2015 [cited 2025 Dec 29]. Available from: https://worldwide.espacenet.com/patent/search/family/037302735/publication/EP1845961B1?q=EP1845961B1.
25. European Patent Office. Application EP06706291 - Rivaroxaban dosing (EP1845961) [Internet]. Munich: EPO Register [cited 2025 Dec 29]. Available from: https://register.epo.org/application?number=EP06706291.
26. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Effects of single-dose BAY 59-7939 - an oral, direct factor Xa inhibitor - in subjects with extreme body weight. Blood. 2005;106(11):1872.
27. Mueck W, Becka M, Kubitza D, Voith B, Zuehlsdorf M. Population model of the pharmacokinetics and pharmacodynamics of rivaroxaban--an oral, direct factor xa inhibitor--in healthy subjects. Int J Clin Pharmacol Ther. 2007;45(6):335-344.
28. Kubitza D, Becka M, Mueck W, Zuehlsdorf M. Multiple dose escalation study investigating the pharmacodynamics, safety and pharmacokinetics of BAY 59-7939, an oral direct Factor Xa inhibitor in healthy male subjects. Blood. 2003;102(11):811a.
29. Boards of Appeal of the European Patent Office. Decision T1732/18 – 3.3.01 [online]. Munich: EPO; 2021 [cited 2025 Dec 29]. Available from: https://www.epo.org/en/boards-of-appeal/decisions/t181732eu1.
30. Meade J. Sandoz AG & Ors v Bayer AG [2024] EWHC 796 (Pat) [online]. London: High Court of Justice; 2024 [cited 2025 Dec 29]. Available from: https://www.bailii.org/ew/cases/EWHC/Patents/2024/796.html.
31. Tribunal judiciaire de Paris. Sandoz SAS v Bayer Intellectual Property GmbH, RG n°22/08612 [online]. Paris: Tribunal judiciaire de Paris; 2024 [cited 2025 Dec 29]. Available from: https://www.courdecassation.fr/en/decision/6605c3ae85819597271e5a19.
32. Rechtbank Den Haag. Bayer Intellectual Property GmbH v Sandoz B.V., ECLI:NL:RBDHA:2023:16452 [online]. The Hague: District Court of The Hague; 2023 [cited 2025 Dec 29]. Available from: https://uitspraken.rechtspraak.nl/details?id=ECLI:NL:RBDHA:2023:16452.
33. Gerechtshof Den Haag. Bayer Intellectual Property GmbH v Sandoz B.V., ECLI:NL:GHDHA:2025:499 [online]. The Hague: Court of Appeal; 2025 [cited 2025 Dec 29]. Available from: https://uitspraken.rechtspraak.nl/details?id=ECLI:NL:GHDHA:2025:499.
34. Oberlandesgericht München. Bayer Intellectual Property GmbH v Sandoz/Stada, 6 U 2277/24 [online]. Munich: Higher Regional Court Munich; 2025 [cited 2025 Dec 29]. Available from: https://www.gesetze-bayern.de/Content/Document/Y-300-Z-GRURRS-B-2025-N-12677.
35. Richter K. Showdown in Munich: Federal Patent Court revokes Xarelto patent [online]. JUVE Patent; 2025 [cited 2025 Dec 29]. Available from: https://www.juve-patent.com/cases/showdown-in-munich-federal-patent-court-revokes-xarelto-patent/.
36. European Patent Office. EP1427415B1 – Lactam-containing compounds and derivatives thereof as Factor Xa inhibitors [online]. Munich: EPO; 2009 [cited 2026 Jan 5]. Available from: https://data.epo.org/publication-server/pdf-document?pn=1427415&ki=B1&cc=EP&pd=20090812.
37. Meade J. Sandoz Ltd v Teva Pharmaceutical Industries Ltd EWHC 822 (Pat) [online]. London: High Court of Justice; 2022 [cited 2026 Jan 5]. Available from: https://www.bailii.org/ew/cases/EWHC/Paten-ts/2022/822.html.
38. Montana M. Barcelona Appeal Court reverses first-instance judgment that had found apixaban patent to be invalid [online]. Wolters Kluwer Patent Blog; 2024 [cited 2026 Jan 5]. Available from: https://patentblog.kluweriplaw.com/2024/07/23/barcelona-appeal-court-reverses-first-instance-judgment-that-had-found-apixaban-patent-to-be-invalid/.
39. Rechtbank Den Haag. Teva v Bristol-Myers Squibb, ECLI:NL:RBDHA:2024:17665 [online]. The Hague: District Court of The Hague; 2024 [cited 2026 Jan 5]. Available from: https://uitspraken.rechtspraak.nl/details?id=ECLI:NL:RBDHA:2024:17665.
40. Rechtbank Den Haag. Bristol-Myers Squibb v Sandoz B.V., ECLI:NL:RBDHA:2024:17666 [online]. The Hague: District Court of The Hague; 2024 [cited 2026 Jan 5]. Available from: https://uitspraken.rechtspraak.nl/details?id=ECLI:NL:RBDHA:2024:17666.
41. Bundespatentgericht. Mepha Pharma AG v Bristol-Myers Squibb Holdings Ireland Unlimited Company [online]. St. Gallen: Swiss Federal Patent Court; 2024 [cited 2026 Jan 5]. Available from: https://www.bundespatentgericht.ch/fileadmin/entscheide/O2022_007-Entscheid_2024-03-05.pdf.
42. Bundesgericht. Mepha Pharma AG v Bristol-Myers Squibb Holdings Ireland Unlimited Company [online]. Lausanne: Swiss Federal Supreme Court; 2024 [cited 2026 Jan 5]. Available from: https://www.bger.ch/ext/eurospider/live/de/php/aza/http/index.php?lang=de&type=highlight_simple_query&page=1&from_date=&to_date=&sort=relevance&insertion_date=&top_subcollection_aza=all&query_words=patent+priorit%E4t+bremi.
43. European Patent Office. EP1173181B1 – Composition comprising phosphodiesterase inhibitors for the treatment of sexual dysfunction [online]. Munich: EPO; 2003 [cited 2026 Jan 6]. Available from: https://www.patentlitigation.ch/themencode-pdf-viewer-sc/?tnc_pvfw=ZmlsZT1odHRwczovL3d3dy5wYXRlbnRsaXRpZ2F0aW9uLmNoL3dwLWNvbnRlbnQvdXBsb2Fkcy8yMDE5LzEwL0VQMTE3MzE4MUIxLnBkZiZzZXR0aW5ncz0xMTExMDExMTExMTEwMSZsYW5nPWVuLVVT.
44. Arnold J. Actavis Group PTC EHF and others v ICOS Corporation and another UKSC 15 [online]. London: UK Supreme Court; 2019 [cited 2026 Jan 6]. Available from: https://www.supremecourt.uk/cases/uksc-2017-0214.html.
45. Bundespatentgericht. Urteil 3 Ni 22/15 (EP) hinzuverbunden 3 Ni 27/15 (EP) [online]. Munich: German Federal Patent Court; 2017 [cited 2026 Jan 5]. Available from: https://www.patentlitigation.ch/themencode-pdf-viewer-sc/?tnc_pvfw=ZmlsZT1odHRwczovL3d3dy5wYXRlbnRsaXRpZ2F0aW9uLmNoL3dwLWNvbnRlbnQvdXBsb2Fkcy8yMDE5LzEwLzAzMDIyXzE1LnBkZiZzZXR0aW5ncz0xMTExMDExMTExMTEwMSZsYW5nPWVuLVVT.

46. Rechtbank Den Haag. Teva v Icos, ECLI:NL: RBDHA:2018:2668 [online]. The Hague: District Court of The Hague; 2018 [cited 2026 Jan 6]. Available from: https://www.patentlitigation.ch/themencode-pdf-viewer-sc/?tnc_pvfw=ZmlsZT1odHRwczovL3d3dy5wYXRlbnRsaXRpZ2F0aW9uLmNoL3dwLWNvbnRlbnQvdXBsb2Fkcy8yMDE5LzEwL0VDTElfTkxfUkJESEFfMjAxOF8yNjY4LnBkZiZzZXR0aW5ncz0xMTExMDExMDExMTExMTEwMSZsYW5nPWVuLVVT.
47. Sø- og Handelsretten. A-49-17 [online]. Copenhagen: Maritime and Commercial High Court; 2018 [cited 2026 Jan 5]. Available from: https://www.patentlitigation.ch/themencode-pdf-viewer-sc/?tnc_pvfw=ZmlsZT1odHRwczovL3d3dy5wYXRlbnRsaXRpZ2F0aW9uLmNoL3dwLWNvbnRlbnQvdXBsb2Fkcy8yMDE5LzEwL0EwMDQ5MDAxLnBkZiZzZXR0aW5ncz0xMTExMDExMDExMTExMTEwMSZsYW5nPWVuLVVT.
48. Markkinaoikeus/Marknadsdomstolen. MAO:131/19 [online]. Helsinki: Market Court; 2019 [cited 2026 Jan 5]. Available from: https://www.markkinaoikeus.fi/fi/index/paatokset/teollisjatekijanoikeudellisetasiat/1553674452924.html.
49. Fierce Pharma. The cardiovascular scene to shift by 2024 as next-generation drugs like Eliquis and Xarelto eclipse stalwarts [online]. Fierce Pharma; 2018 [cited 2026 Jan 7]. Available from: https://www.fiercepharma.com/pharma/cardiovascular-landscape-from-2017-to-2024-featuring-eliquis-xarelto-and-more.
50. Grand View Research. Eliquis (Apixaban) Market Size, Share & Trends Analysis Report by Indication (Atrial Fibrillation, DVT, PE), Distribution Channel, Region, Global Forecast 2025–2033 [online]. San Francisco: Grand View Research; 2025 [cited 2026 Jan 7]. Available from: https://www.grandviewresearch.com/industry-analysis/eliquis-apixaban-market-report.
51. Alanazi AA, Alotaibi A, Alzarea AI, Ahmed D, Alqahtani SS, Althobaiti YS. Factors associated with inappropriate apixaban dosing persistence in non-valvular atrial fibrillation patients at a university teaching hospital in Riyadh, Saudi Arabia. Farmacia. 2025;73(3):569-578.
52. Eli Lilly and Company. 2017 Annual Report [online]. Indianapolis (IN): Eli Lilly and Company; 2018 [cited 2026 Jan 7]. Available from: https://investor.lilly.com/node/38271/pdf.
53. Community Pharmacy England. Rivaroxaban tablets – changes to reimbursement from September 2024 [online]. London: Community Pharmacy England; 2024 [cited 2026 Jan 7]. Available from: https://cpe.org.uk/our-news/rivaroxaban-tablets-changes-to-reimbursement-from-september-2024/.
54. WaveData. Huge price spikes of Apixaban 5 mg 56 drive investigation of the long-term view of both the generic and brand [online]. WaveData; 2024 [cited 2026 Jan 7]. Available from: https://www.wavedata.co.uk/huge-price-spikes-of-apixiban-5mg-56-drive-investigation-of-the-long-term-view-of-both-the-generic-and-brand/.
55. NHS Business Services Authority. Drug Tariff Part VIIIA: June 2017 [online]. Newcastle: NHSBSA; 2017 [cited 2026 Jan 7]. Available from: https://www.nhsbsa.nhs.uk/sites/default/files/2017-06/drug-tariff-part-viiia-june-2017.pdf.
56. NHS Business Services Authority. Drug Tariff Part VIIIA: March 2020 [online]. Newcastle: NHSBSA; 2020 [cited 2026 Jan 7]. Available from: https://www.nhsbsa.nhs.uk/sites/default/files/2020-02/Drug%20Tariff%20Part%20VIIIA%20March%202020.pdf.
57. Deutsche Apotheker Zeitung. Patentgericht widerruft Xarelto-Patent [online]. Deutsche Apotheker Zeitung; 2025 [cited 2026 Jan 10]. Available from: https://www.deutsche-apotheker-zeitung.de/autoren/news/artikel/2025/08/01/patentgericht-widerruft-xarelto-patent.
58. European Commission. Pharmaceutical Strategy for Europe [online]. Brussels: European Commission; 2020 [cited 2026 Jan 10]. Available from: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en.
59. Frakes MD, Wasserman MF. Strategic Patenting: Evidence from the Biopharmaceutical Industry [online]. NBER Working Paper No. 34024. Cambridge (MA): National Bureau of Economic Research; 2025 [cited 2026 Jan 11]. Available from: https://www.nber.org/papers/w34024.
60. Organisation for Economic Co-operation and Development (OECD). Pharmaceutical Innovation and Access to Medicines [online]. Paris: OECD Publishing; 2018 [cited 2026 Jan 11]. Available from: https://doi.org/10.1787/9789264307391-en.
61. Unified Patent Court. UPC Member States [online]. Luxembourg: Unified Patent Court; [cited 2026 Jan 11]. Available from: https://www.unifiedpatentcourt.org/en/organisation/upc-member-states.
62. European Patent Office. Unitary Patent Guide, Part A (V) – The benefits of the Unitary Patent [online]. Munich: EPO; 2024 [cited 2026 Jan 11]. Available from: https://www.epo.org/en/legal/guide-up/2024/uppg_a_v.html.
63. European Patent Office. Frequently Asked Questions: What are the benefits of the Unitary Patent? [online]. Munich: EPO; [cited 2026 Jan 10]. Available from: https://www.epo.org/en/service-support/faq/law-practice/unitary-patent/general-information/what-are-benefits-unitary.
64. European Patent Office. Frequently Asked Questions: What are the arrangements for the transitional period (opt-out scheme and choice of forum) for the Unified Patent Court? [online]. Munich: EPO; [cited 2026 Jan 11]. Available from: https://www.epo.org/en/service-support/faq/law-practice/unified-patent-court/what-are-arrangements-transitional-period-opt.