



Repositioning Generic Drugs: Empirical Findings and Policy Implications

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Abstract Commentators claim that drug repositioning (i.e. developing new uses for authorised drugs) significantly slows when generics are authorised and, therefore,

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law reform is necessary to encourage more R&D. This study empirically examines this claim by analysing records of clinical trials. It finds that once generics are authorised: (i) commercial trials continue at “active” rates for approximately half of the drugs studied, and (ii) the number of hospital and university trials actually increases. These findings cast doubt on whether additional incentives are needed. They also indicate that a more effective way to reposition drugs is for recently established government programmes to embrace IP strategies and leverage the hospital and university trials as an R&D pipeline.

Keywords Drug repositioning · Patent law · Regulatory protection · Clinical trials · Empirical study · Generic drugs

1 Introduction

Generic drugs are considered indispensable to healthcare systems because they are substantially cheaper than original versions of the drugs.¹ Yet, high-profile commentators on both sides of the North Atlantic claim that the availability of generics carries a significant detriment: that research on new uses of the compounds becomes financially unviable and, therefore, significantly slows or stops.² These claims refer to challenges of obtaining and enforcing intellectual property (IP),³ which are detailed in the following section “Background”. Areas of research that lack IP incentives are often referred to as “gaps”, and many commentators argue that the gap for new uses is so significant that law reform is required.⁴

Developing and obtaining authorisations for new uses of existing drugs, an area of research known as “repositioning”,⁵ has great potential for society. Repositioning is often faster, less expensive and lower risk than developing new compounds. Much is already known about the drugs, including safety profiles and how the compounds achieve their therapeutic effects.⁶ Estimates suggest repositioning is 40–90% cheaper than developing new compounds.⁷ Thus, repositioning has great potential for both patients and healthcare systems.

If an innovation gap does open for repositioning when generics are authorised, then society should consider closing it. Commentators have suggested various law and policy reforms, including lengthening the term of IP rights or introducing new ones.⁸ However, attempting reform without rigorous evidence, including empirical

¹ European Commission (2009), Pharmaceutical Sector Inquiry: Final Report at https://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf (accessed 17 August 2021).

² See e.g., Breckenridge and Jacob (2019), p. 2; Eisenberg (2005), pp. 720–725.

³ See the “Background” section of this article.

⁴ See e.g., Breckenridge and Jacob (2019), p. 2; Cordery and Willis (2017), p. 28.

⁵ See e.g., Liddicoat et al. (2021a), p. 828.

⁶ Oprea and Mestres (2012), p. 759.

⁷ Grabowski and Moe (2008), p. 85; Brief for Allergan, Inc et al. as Amici Curiae supporting Respondents, 8 in *Caraco Pharmaceutical Laboratories Ltd v. Novo Nordisk A/S* (2012) 566 U.S. 399 (2012).

⁸ See e.g., Breckenridge and Jacob (2019), p. 2; Cordery and Willis (2017), pp. 28–29.

evidence, can be a perilous path. The reform might fail to achieve its aim or produce counterproductive results, enabling companies to charge higher prices for longer.⁹

Two empirical studies have looked at repositioning activity by examining registers of authorised drugs. Both studies find that new uses are added shortly after drugs are initially authorised and that significantly fewer uses are added once generics are authorised. These findings support the standard view that repositioning research significantly slows after generic entry, and the authors suggest strengthening IP and other aspects of pharmaceutical regulation to encourage more repositioning.¹⁰ Yet, empirical methods evolve over time, and both studies have two limitations. First, neither considers combining a compound with another as repositioning, which suppresses the repositioning count and is contrary to established repositioning strategies.¹¹ Second, both studies measure the outcomes of research in the form of additional authorisations for new indications as a proxy for research activity.¹² This underestimates research activity when drugs fail new-use trials or authorisations are not pursued due to a change in priorities.

This study aims to overcome these weaknesses by (i) defining repositioning to include all new uses of the compounds, including new combinations with other molecules; and (ii) examining the number of *clinical trials* for a cohort of compounds from initial authorisation until five years after generics are authorised. If repositioning research significantly slows after generic entry, as previous studies have concluded, then the clinical trial data in this study should show developers conducting clinical trials shortly after the drugs are authorised and this activity decreasing to a minimal level as the authorisation of the generics approach.

The data confirm some aspects of earlier studies but also yield two unexpected results. Similar to earlier studies, the data show that trials by originators (the companies that initially obtained authorisations for the drugs) peak around eight years before authorisation of the generics and then slow to almost zero by three years before the generics are authorised. The first unexpected result is that trials conducted by competitors (companies other than originators and their allies) *increase* after the generics are authorised. Indeed, this study finds that competitors repositioned two of the 15 drugs (13%) in this study *after* the generics were authorised, and one of the compounds was repositioned twice. Two of the three repositioned uses combine the generic compound with another molecule. Second, the number of trials conducted by hospitals and universities *increase* after generic authorisation. This is best demonstrated by the result that the total number of repositioning trials conducted by hospitals and universities in the five years *after* generic entry is higher than the total number of trials conducted by originators during *any* five-year period.

Commentary on how to increase the number of repositioned drugs typically focusses on reform to IP and pharmaceutical law. However, this study shows that this focus might be misplaced because existing incentives are working better than

⁹ See e.g., Liddicoat et al. (2021a), pp. 833 and 944.

¹⁰ Langedijk et al. (2016), pp. 349, 352 and 354; Sahragardjoonegani et al. (2021), pp. 3–7.

¹¹ See generally, Lee (2012).

¹² Langedijk and colleagues acknowledge this weakness, see: Langedijk et al. (2016), p. 354.

first thought and any reform is likely to be costly and potentially detrimental (i.e. it may not lead to a material increase of authorised new uses). Moreover, the data on hospital and university trials indicate a potentially better option for repositioning, building on two recently established European government programmes. One programme is conducted by the European Commission Expert Group on Safe and Timely Access to Medicines for Patients and another by the several government departments in England, including the National Health Service. These programmes currently focus on repositioning drugs that are commonly used “off-label”, that is, drugs that are used for a purpose that has not been authorised.¹³ This study, though, suggests that these programmes could be more ambitious: using clinical trials conducted by hospitals and universities as an R&D pipeline for repositioning relatively large numbers of generic drugs. In other words, the programmes could work synergistically with hospitals, and universities could become leaders in generic-drug repositioning.

This paper is divided into five parts. Following this introduction, part two provides background information on various aspects of drug authorisation processes in the US and Europe. Part three describes this study’s research questions and methods, and part four describes the results. Part five discusses the policy implications arising from the results, casting doubt on the need for IP and pharmaceutical law reform. It also suggests that the European programmes could capitalise on the substantial number of hospital and university clinical trials by incorporating IP and commercialisation strategies.

2 Background

2.1 Authorisation Processes in the US and Europe

This study focuses on generics of small molecules classified as new chemical entities (NCEs) when they were initially authorised.¹⁴ Regulatory authorisations of NCEs (and any subsequent new uses) in the US, UK and EU require the successful completion of clinical trials.¹⁵ Typically, regulators require data from phase I, II and III trials. Phase I trials assess the safety of a drug and how the drug is metabolised in a small number of patients or healthy volunteers (approx. 10 to 20 people).¹⁶ If patients are involved, the trials may test the drug in multiple medical conditions in a

¹³ European Commission Expert Group on Safe and Timely Access to Medicines for Patients (2017), pp. 3–4; Medicines Repurposing Programme Board, “Opportunities to Repurpose Medicines in the NHS” (February 2021) 5–6, at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021).

¹⁴ 21 C.F.R. § 314.108(a).

¹⁵ In the US, NCEs are authorised under 21 U.S.C. § 355(b)(1), in Europe they are authorised under Directive 2001/83/EC (OJ L 311 p. 67), Art. 8(3), and in the UK under The Human Medicines Regulation 2012, reg. 49.

¹⁶ Middleton (2015), p. 46; Cancer Research UK (2022), Phases of Clinical Trials at <https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are/phases-of-clinical-trials> (accessed 2 June 2022).

shot-gun approach, especially if the compound potentially treats cancer.¹⁷ Phase II trials continue to assess the safety of the drug and look at efficacy in medium-sized patient cohorts (approx. 100 people). Phase III trials also look at safety but focus more on efficacy in large patient cohorts (often hundreds or sometimes thousands of people).¹⁸ This study only analyses phase II and phase III trials.

The authorisation of generics is tightly regulated in the US. In general, the US Food and Drug Administration (FDA) can accept a generic application only if at least five years have elapsed since the initial authorisation of an NCE.¹⁹ In a scenario in which a drug is patent protected and a generic company plans to challenge the patent (or patents) on the basis of invalidity or noninfringement, the FDA can *accept* a generic application after four years. However, the time before the FDA can *authorise* the generic application depends on whether the originator begins litigation.

When a patent protects a drug, the applicant must agree to wait until the patent expires or assert either that its product will not infringe the patent or that the patent is invalid.²⁰ Such assertions are known as “Paragraph IV certifications”.²¹ If the originator contests (i.e. litigates) the Paragraph IV certification within 45 days of receiving notice, the originator is granted a stay that stops the FDA from authorising the generic application for an additional 30 months,²² which means that the application generally cannot be authorised for at least 7.5 years, unless litigation resolves sooner. A study on Paragraph IV certifications shows that about one-third of generic applications result in a 30-month stay.²³ Although stays might be expected to delay the marketing of generics, the study also found that these stays nearly always expire “well before” generic entry, suggesting that factors other than the stay (such as that FDA review of the generic drug application has not yet been completed) control the time of generic entry.²⁴

The authorisation of generics in the EU and UK is simpler than in the US. The UK and EU have the same time frames, as the UK system is modelled on the EU system. Originators are granted eight years of data protection, which stops regulators from accepting applications for generics until the period expires. Originators are also granted ten years of market protection, which means that generic drugs can be authorised after the data protection expires but *not marketed* until two years later.²⁵

¹⁷ Cancer Research UK (2022), Phases of Clinical Trials at <https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are/phases-of-clinical-trials> (accessed 2 June 2022).

¹⁸ Middleton (2015), pp. 46–47; Cancer Research UK (2022), Phases of Clinical Trials at <https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/what-clinical-trials-are/phases-of-clinical-trials> (accessed 2 June 2022).

¹⁹ 21 C.F.R. § 314.108(b)(2).

²⁰ 21 C.F.R. § 314.50(i)(1)(i)(A)(4).

²¹ Kannappan et al. (2021), p. 1918.

²² 21 U.S.C. § 355(c)(3)(E)(ii).

²³ Kannappan et al. (2021), pp. 1922–1924.

²⁴ *Ibid.*

²⁵ Directive 2001/83/EC (OJ L 311 p. 67), Art. 10(1); The Human Medicines Regulation 2012, Reg. 51.

2.2 The Gap: IP and Financial Incentives for Repositioning

This article uses records of clinical trials to critically examine the alleged innovation gap for generic drug repositioning. Such a gap would mean that society is not fully benefiting from treatments that could be developed faster, cheaper and safer than the development of new compounds. The alleged cause for this gap is insufficient IP protection, which affects financial incentives. Repositioning a generic drug is likely to be cheaper than developing a new compound. However, it is still likely to cost at least US\$100 million,²⁶ and there is no guarantee of success. Thus, drug developers often seek IP to help ensure they can secure returns on their investments.²⁷

Typically, drug developers seek patents for the new use. However, patents are said to offer relatively weak protection for repositioning. The weakness stems from rules about patent eligibility and enforcement as well as aspects of the way drugs are labelled, prescribed, dispensed, and reimbursed around the globe. The arguments articulating the weakness can be divided into two issues and have been restated and elaborated on in various ways for over 15 years in multiple jurisdictions.²⁸

The first issue concerns the requirements that must be met for a patent to be granted and avoid revocation. Patents are only valid for *novel* inventions (not previously available to the public).²⁹ Consequently, patents for repositioned drugs might be difficult to obtain (or are revocable) because the new use is already described in scientific literature.³⁰ Another requirement for a valid patent is that the invention involves an inventive step,³¹ which requires that the invention is *not* obvious based on prior knowledge available to the public.³² However, it is not always clear whether a new use is inventive in light of the existing science, especially when it is known that some drugs bind to molecules involved in several diseases.³³ A third challenge for the validity of a new-use patent is that many territories require that sufficient information be disclosed in the application at the date it is filed.³⁴ For example, the European Patent Office (EPO) and various contracting states to the European Patent Convention require that applications provide evidence showing that the drug could *plausibly* treat the disease.³⁵ This

²⁶ Grabowski and Moe (2008), p. 85.

²⁷ Cordery and Willis (2017), p. 25.

²⁸ See e.g., Eisenberg (2005), pp. 720–735; Lietzan (2018), pp. 177–191; Breckenridge and Jacob, (2019), p. 2.

²⁹ European Patent Convention 1973 Art. 54.

³⁰ Breckenridge and Jacob (2019), p. 2; Eisenberg (2005), p. 724; Roin (2009), pp. 517–531; Pushpakom et al. (2018), pp. 50–51.

³¹ European Patent Convention 1973 Art. 56.

³² Breckenridge and Jacob (2019), p. 2; Eisenberg (2005), p. 724; Roin (2009), pp. 531–545; Pushpakom et al. (2018), pp. 50–51.

³³ Roin (2009), pp. 544–545.

³⁴ This includes the US, see, Breckenridge and Jacob (2019), p. 2.

³⁵ European Patent Office 2019, Case Law of the Boards of Appeal, “7.2 Level of Disclosure Required for Medical Use – Plausibility” at https://www.epo.org/law-practice/legal-texts/html/caselaw/2019/e/clar_ii_c_7_2.htm (accessed 2 June 2022). Plausibility is not a standalone requirement for a valid patent. Rather, it is a principle that is relevant to various aspects of patent law, including inventive step,

raises two problems. The first is that applications with *insufficient* data will be refused. The second is that generating this evidence may take significant time, during which the use might be disclosed in scientific literature (meaning the patent is no longer novel) or the science advances to the point where the treatment is obvious (meaning the patent no longer involves an inventive step).

A recent article has empirically analysed the difficulty of obtaining new-use patents by studying data from the EPO. The study indicates that patents for new uses are easier to obtain than previously thought. One of its main findings is that patent applications and grants for new uses have generally been increasing over the last decade.³⁶ It also found that the percentage of granted new-use applications was similar or higher than applications for other technologies.³⁷ There is little doubt that the requirements for a patent (i.e. novelty, inventive step, etc.) will stop some applications from being granted. However, this study shows that obtaining patents for new uses is increasingly common and granted at rates similar to other technologies.³⁸

Although the issue of patent eligibility may not be as challenging for developers as first thought, the issue of difficulty in enforcement remains. Indeed, Breckenridge and Jacob (a former chair of a regulatory agency and a retired appellate judge, respectively) suggest it is probably the most important.³⁹ The issue concerns how drugs are labelled, prescribed and dispensed. *If* a developer obtains a regulatory authorisation for the new use of a generic drug, then pharmacists will stock the developer's latest version alongside generic versions. The developer's version will include the new use on the label, and the developer would likely obtain a patent for the new use, which would prevent the generics from including the new use on their labels. However, the difference in labels does not prevent generics from being dispensed for the new use in practice. Doctors commonly prescribe drugs by international non-proprietary names (INNs),⁴⁰ and pharmacists then dispense them relying on INNs without direct knowledge of their patients' diagnoses.⁴¹ Health systems financially encourage pharmacists to dispense generics because the generics are cheaper and, since pharmacists do *not* know their patients' diagnoses, they often dispense generics for uses that are patented.⁴² Although patients *could* be liable for

Footnote 35 continued

sufficiency, and industrial applicability. For a review, *see*, England (2014). Not all Member States have imported the concept of plausibility, but they do apply similar criteria, *see*, for example, Ackermann (2021), pp. 4–5.

³⁶ Aboy et al. (2021), pp. 1338–1340; *see also*, Aboy et al. (2022).

³⁷ *Ibid.* 1338.

³⁸ *Ibid.* 1343.

³⁹ Breckenridge and Jacob (2019), p. 2.

⁴⁰ World Health Organization n.d., Guidance on INN at <https://www.who.int/teams/health-product-and-policy-standards/inn/guidance-on-inn> (accessed 2 June 2022).

⁴¹ Breckenridge and Jacob (2019), p. 2; England (2016), pp. 427–431; *Warner-Lambert Co LLC v Generics (UK) Ltd* [2019] 3 All ER 95 at [65]–[66]. Denmark is an exception to this comment, where prescriptions include the diagnoses, *see*, Kilpatrick (2019).

⁴² *Ibid.*

infringing the patent, direct enforcement against patients has not occurred anywhere to the authors' knowledge.

The scenario of generic drugs being dispensed for patented new uses has recently become known as “cross-label” use.⁴³ Cross-label use is a subcategory of off-label use (mentioned above). Cross-label use describes the use of a generic drug to treat a condition that another company has obtained authorisation for from a regulator, in circumstances where the generic drug's label omits the use because the use is subject to patent protection.⁴⁴ In contrast, off-label use refers to the use of a drug that has been authorised for at least one condition but not for the condition it is prescribed for.

Pharmaceutical companies have sued generic companies based on cross-label use in various jurisdictions. The law is complex. However, many important markets, including the US, UK, France and Germany, have absolved generic companies of liability, as long as they do not advertise or specifically produce the drug for the patented purpose and take steps to avoid cross-label use, such as informing medical professionals that their authorisations are limited to specific non-patented uses.⁴⁵

Developers that reposition drugs typically obtain regulatory IP in addition to patents. In theory, the regulatory IP could help secure returns on their investments, but this IP is typically thought to be insufficient too. In the US, drug developers obtain three years of protection if their drug is authorised for a new indication and they conducted new clinical investigations to support the new indication.⁴⁶ The protection stops the FDA from approving generic applications for the new use. However, commentators argue that this period is too short.⁴⁷ Further, the exclusivity only prevents the FDA from authorising a generic application for that *specific indication*. Drug developers can obtain generic authorisations for the initial indication, and the availability of these generics raises the possibility of cross-label use.⁴⁸

Regulatory IP in the UK and EU differ depending on whether the developer already holds an authorisation for the compound. As mentioned, UK and EU law grant eight years of data protection and ten years of market protection when a drug is initially authorised. What was not mentioned, though, is that the ten years of market protection can be extended to 11 if the compound is repositioned for a new indication that significantly improves clinical care.⁴⁹ The extension of market protection stops companies from marketing their generics for the new *and* the old

⁴³ Cordery and Willis (2017), p. 26; Lunze (2014); Bühling (2016a), p. 53.

⁴⁴ And, thus, another company has the exclusive rights to advertise, sell, and use the drug for the medical indication.

⁴⁵ *Warner-Lambert Co LLC v Generics (UK) Ltd* [2019] 3 All ER 95 at [84]–[86], [218]; Altman (2016), pp. 34–36; Bühling (2016b), pp. 56–61; Romet and Talvard (2016), pp. 126–130; *see also*, Simmons and Simmons (2019), Infringement of Swiss-type second medical use claims at <https://www.simmons-simmons.com/en/publications/ck0am31acner80b858w0vy9is/280119-infringement-of-swiss-type-second-medical-use-claims> (accessed 2 June 2022).

⁴⁶ 21 U.S.C. § 355(j)(5)(F)(iv).

⁴⁷ Cordery and Willis (2017), p. 27.

⁴⁸ Lietzan (2018), pp. 180–191.

⁴⁹ Directive 2001/83/EC (OJ L 311 p. 67), Art. 10(1); The Human Medicines Regulation 2012, Reg. 51.

uses.⁵⁰ However, it is only one year of extra protection, which commentators describe as insufficient.⁵¹

A lesser-known aspect of EU and UK law applies when developers want to reposition other companies' drugs and do *not* already hold an authorisation for the compound.⁵² These developers can obtain eight years of data protection and ten years of market protection (with the possibility of extension to 11) on the authorisation of a new use.⁵³ That said, the protection only covers the indications the developer applied for;⁵⁴ the protection does *not* provide a power to stop generic authorisations for the original use (obtained by another developer). The lack of power to stop the marketing of generics for other uses means that these developers have no power to stop cross-label use.

Breckenridge and Jacob describe cross-label use as perhaps the most important issue hindering repositioning. Moreover, they state that “if a generic version of a drug is available, developers have little or no opportunity to recoup their investment in the development of the drug for a new [use].”⁵⁵ In essence, the commentators are saying that if a drug developer conducts a clinical trial for a new use, they have a slim chance of obtaining revenue that will cover the costs of the trial.

3 Research Questions and Methods

3.1 Research Questions and an Overview of the Study

This study was motivated by two considerations. First, Breckenridge and Jacob's statement that new use developers have little or no opportunity to recoup their investments after a generic version of the drug is available and, second, the dearth of robust data on repositioning after generic authorisation. Consequently, this study addresses the following research questions:

1. How do the numbers of clinical trials aimed at repositioning drugs vary from initial authorisation until five years after generic authorisation?
2. Does the number of trials significantly slow or stop after generics are authorised? and
3. Which organisations are conducting the trials?

The general idea behind questions 1 and 2 is to compare the number of trials per year after generic authorisation with the number before. The comparison will divide the data into two time periods: (i) the “exclusivity period”, referring to the time

⁵⁰ Directive 2001/83 Arts. 6(1) and 10(1); European Commission 2019 at https://ec.europa.eu/health/system/files/2019-07/vol2a_chap1_en_0.pdf (accessed 2 June 2022), pp. 9–10 and 43.

⁵¹ Breckenridge and Jacob (2019), p. 2; Cordery and Willis (2017), p. 27.

⁵² See e.g., Pushpakom et al. (2018), pp. 51–52.

⁵³ Directive 2001/83/EC (OJ L 311 p. 67), Arts. 8(3) and 10(1); The Human Medicines Regulation 2012, Regs. 49 and 51.

⁵⁴ Directive 2001/83/EC (OJ L 311 p. 67), Art. 10(1).

⁵⁵ Breckenridge and Jacob (2019), p. 2.

when the originators had the only authorisations for the compounds; and (ii) the “generic period”, referring to the time after the generics were authorised. All drugs have different initial authorisation and generic authorisation dates; therefore, the comparisons will be drawn between individual drugs.⁵⁶

This study uses a typology with four categories to compare individual drugs. The typology was devised by three authors (JL, KL and JD) *before* the analysis began as a way to summarise the study’s findings. Three categories describe the relative number of trials: (i) “lower”, which means the number of trials per year during the generic period is less than or equal to half (i.e. $\leq 50\%$) the number of trials per year during the exclusivity period; (ii) “active”, which means the numbers of trials per year during the generic period is greater than half and less than double (i.e. $> 50\%$ and $< 200\%$) the number of trials per year during the exclusivity period; and (iii) “higher”, which means the number of trials per year during the generic period is equal to or greater than double (i.e. $\geq 200\%$) the number of trials per year during the exclusivity period. A fourth category, “unclassified”, describes drugs that have too few clinical trials to meaningfully classify; in this case, compounds that have equal to or less than one trial every two years.

3.2 The Generic Drugs Studied

This study analyses clinical trials for NCEs with generics authorised for the first time in the US in 2014. The idea is that one year should provide enough drugs to observe trends in clinical trial activity, and 2014 was the most recent full year that could be analysed when this project began (if five years of activity is to be observed). This study tracks all the phase II and phase III clinical trials conducted anywhere in the world for these compounds and uses US authorisation dates because the US is the largest nation by drug expenditure and, therefore, authorisation in the US likely has the most significant impact on IP and financial incentives for repositioning.⁵⁷

This study only analyses products that had three characteristics: (i) the products contained compounds that were NCEs when they were initially authorised in the US; (ii) a generic version of the compound in the product was authorised for the first time in any form (e.g. strength or formulation) in the US in 2014; and (iii) competitors did *not* market a version of the compound in the US (such as by filing a completely new drug application rather than an abbreviated new drug application) until after the generic was authorised. These characteristics ensure that during the exclusivity period the originators had complete market exclusivity for the compound and that this situation changed only when the generic was authorised.

⁵⁶ An analyst at Trialrove said that the database had less comprehensive coverage of clinical trials for some drugs authorised in the early and mid-1990s. Two drugs drug in this study, rifabutin and ropivacaine, were initially authorised in the mid-1990s, yet the drug’s first trial commenced several years later, in 1999 and 2000 respectively. When calculating the number of trials per year for these drugs, the study calculated the exclusivity period as beginning on the day the first trial began, not when the drugs were initially authorised.

⁵⁷ World Health Organization n.d., Global Health Expenditure Database at <https://apps.who.int/nha/database/Select/Indicators/en> (accessed 2 June 2022).

The FDA creates an annual list of “first generics”, which records the first time a generic for a particular drug product was authorised in that year. The FDA’s 2014 list of first generics contains 96 generic products,⁵⁸ but many refer to the same compound in different forms (e.g. in different formulations or strengths). To avoid a type of double counting, multiple forms of the same compound were reduced to a unique single entry. The FDA’s list also contains products that lack the first two characteristics; namely, products that were: (i) generics of products that were *not* NCEs when they were first authorised (such as those authorised when a competitor submits a new drug application rather than an abbreviated new drug application); and (ii) different forms of compounds that were already generic (e.g. a different strength was authorised in 2013). This study removed the non-NCEs as well as the compounds that already had a generic available. This process yielded 19 unique compounds.

Four additional compounds were removed from this list of 19 compounds because they lacked the third characteristic. Generics of these four compounds were first authorised in 2014. However, *competitors* marketed new products containing the compounds *before* the generics were authorised. Drug developers can achieve this in the US via either full, new drug applications or hybrid applications called “505(b)(2) applications”, which allow applicants to submit applications that partially rely on originators’ data.⁵⁹ These compounds were removed from the list because the hybrid applications meant a competing version of the drug was on the market before the generic was authorised. Once these were removed, 15 compounds remained, which were the subject of this study.

3.3 Clinical Trial Data

Records of clinical trials with these 15 compounds were downloaded from the database Trialrove. The database is advertised as the “most comprehensive, accurate and up-to-date source of pharmaceutical trials data”.⁶⁰ The downloaded data included all records of phase II and III trials for the compounds tested as the “primary drug”⁶¹ between the time when the compounds were initially authorised and 30 March 2020, when the data were downloaded. In total, data on 2,293 clinical trials were downloaded, which included information on trial phase, participants,

⁵⁸ U.S. Food and Drug Administration (2015) ANDA (Generic) Drug Approvals at <https://wayback.archive-it.org/7993/20170112074441/http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm430850.htm> (accessed 2 June 2022).

⁵⁹ 21 U.S.C. 355(b)(2); 21 C.F.R. § 314.108(b)(2). For more information, see Darrow et al. (2019). To qualify for this pathway, applicants must not have authorisation from originators to rely on their data and data exclusivity periods must have expired. However, originators may still have other IP that applicants must license or risk infringing.

⁶⁰ PharmaIntelligence (n.d.) at <https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/trialrove> (accessed 24 August 2021).

⁶¹ Some trials were labelled as phase I/II, II/III, or III/IV. These trials were classified as phase II, III and III, respectively, as the trials were deemed to have reached each of the respective stages.

start dates, trial objectives, and trial sponsors (the organisations that financed the trial, as reported in the public domain).⁶²

This study focusses only on treatments for medical conditions that afflict adults because incentive structures for paediatric patients are different. Legislation in many countries obliges organisations to conduct paediatric trials in certain circumstances (for example, if a drug developer obtains an EU authorisation to treat adults and the drug might also treat children).⁶³ These laws mean that some organisations are effectively compelled to reposition their drugs for paediatric indications,⁶⁴ whereas no such laws exist for adult populations. Consequently, 229 paediatric trials were removed from the data set.

Whilst the data set was reviewed for paediatric trials, the close reading of the clinical trials revealed several other types of trials that were not applicable to this study, leading to the removal of an additional 122 trials. These consisted of phase II bioequivalence studies (used for the authorisation of generics) or trials that tested a derivative compound with different properties.⁶⁵ The remaining 1,954 trials were included in the study. Table 1 provides a summary of the number of trials for each drug and a summary of the originators' indications, including the dates they were authorised.

3.4 Manual Classification of Clinical Trial Data

Each clinical trial was manually classified according to two criteria: (i) sponsorship, which involved reviewing what organisation sponsored the trial; and (ii) type, which involved analysing whether the trial was aimed at treating a condition for which the compound was already authorised.

Four categories were used to describe sponsorship: (a) originators (and their allies), (b) competitors, (c) governments,⁶⁶ and (d) hospitals and universities (including research institutes).⁶⁷ Originators' allies were identified using information on Pharmaprojects, a database associated with Trialrove that tracks companies' development agreements, including licences, mergers and acquisitions.⁶⁸ Companies were identified as competitors after consulting Pharmaprojects and conducting

⁶² Trialrove n.d., Trial Benchmarking, Sitetrove & Citeline Engage Glossary at <https://citeline.zendesk.com/hc/en-us/articles/360017923593-Trialrove-Trial-Benchmarking-Sitetrove-Citeline-Engage-Glossary> (accessed 24 August 2021). This site is only accessible through the online database, however, the corresponding author has a copy of the glossary on file.

⁶³ Council Regulation (EC) No 1901/2006 (OJ 2006 L 378 p.1) Arts. 8 and 9.

⁶⁴ Liddicoat et al. (2021a), pp. 837–838.

⁶⁵ The study analysed the compound sirolimus and the downloaded data included trials with the derivative temsirolimus. MacKeigan and Krueger (2015), pp. 1553–1554.

⁶⁶ Typically identified by the names such as “Department of Health”, “Ministry of X”, “National Institute of X” or other similar titles.

⁶⁷ Typically identified by names such as “university”, “hospital” or “cancer centre”. How these organisations were funded was not investigated. Some would have been funded by governments, whilst others by private organisations.

⁶⁸ Pharmaprojects n.d., Track Pharma R&D at <https://pharmaintelligence.informa.com/products-and-services/data-and-analysis/pharmaprojects> (accessed 24 August 2021).

Table 1 Summary of each drug, including INNs, originators' authorised indications, and the number of adult clinical trials

#	Compound name (INN)	Summaries of the originators' authorised indications (and authorisation dates)	# trials
1	Sirolimus	Prevention of organ rejection (15 Sept 1999)	327
2	Rifabutin	Prevention of mycobacterium avium complex disease (23 Dec 1992)	18
3	Solifenacin succinate	Treatment of overactive bladder (19 Nov 2004)	35
4	Omega-3-acid ethyl esters	Reduction of triglyceride levels (10 Nov 2004)	40
5	Atazanavir sulphate	Treatment of HIV-1 infection (20 June 2003)	48
6	Celecoxib	Treatment of osteoarthritis, and rheumatoid arthritis (31 Dec 1998) Reduction of colorectal polyps (23 Dec 1999) Management of acute pain (18 Oct 2001) Treatment of primary dysmenorrhea (18 Oct 2001) Treatment of ankylosing spondylitis (29 July 2005)	309
7	Erlotinib hydrochloride	Treatment of non-small cell lung cancer (18 Nov 2004) Treatment of pancreatic cancer (2 Nov 2005)	503
8	Valsartan	Treatment of hypertension (23 Dec 1996) Treatment of heart failure (14 Aug 2002) Reduction of cardiovascular mortality after a myocardial infarction (3 Aug 2005)	158
9	Ropivacaine hydrochloride	Local anaesthesia prior to surgery, and management of acute pain (24 Sept 1996)	179
10	Bexarotene	Treatment of cutaneous T-cell lymphoma (29 Dec 1999)	33
11	Dexmedetomidine hydrochloride	Sedation of intubated and mechanically ventilated patients in intensive care (17 Dec 1999) Sedation of non-intubated patients prior to or during surgery (17 October 2008)	177
12	Entecavir	Treatment of chronic hepatitis B infection (29 Mar 2005)	38
13	Frovatriptan succinate	Treatment of acute migraines (8 Nov 2001)	7
14	Daptomycin	Treatment of complicated bacterial skin infections (12 Sept 2003) Treatment of staphylococcus aureus bloodstream infections (25 May 2006)	29
15	Bimatoprost	Treatment intraocular pressure (16 Mar 2001) Treatment of hypotrichosis (24 Dec 2008)	53
Total			1954

Google searches for agreements between the third-party companies and the originator. If a third party conducted trials before they were affiliated with the originator, the trials were classified as sponsored by a competitor, but trials after the affiliation were classified as originator trials (unless the affiliation ended).

Trials were classified as sponsored by one type of organisation only, even if two (or more) different organisations were listed as sponsors (e.g. an originator and a government). If organisations from two categories sponsored a trial, this study used a preferential hierarchy to determine sponsorship: (a) originators, (b) competitors, (c) governments, and (d) hospitals and universities. This hierarchy means that if an originator and a government sponsored a trial, it was classified as sponsored by the originator. But if a government and a hospital sponsored a trial, it was categorised as government. In short, this study first recognised sponsorship by originators, then competitors, then governments and, finally, hospitals and universities.

The manual classification by type sorted the clinical trials into two categories: (i) same-condition (SC) trials; or (ii) new-condition (NC) trials. NC repositioning is typically what commentators think of when they discuss repositioning, and limiting the analysis to NC trials makes the study a more specific and conservative estimate of drug repositioning activity.⁶⁹ Thus, the remainder of this paper focuses on NC trials, and subsequent references to trials are to NC trials unless stated otherwise.

This study used a classification adapted from a recent study of repositioning in Europe to distinguish between SC and NC trials.⁷⁰ The category “SC trials” refers to studies that aimed to treat a new or expanded patient cohort suffering from a condition that the FDA had already authorised for the drug. This category also includes trials that looked for new biomarkers or combined the compound with another molecule, provided the same condition was still being treated. In contrast, the category “NC trials” refers to studies aimed at using the compound to treat a condition for which the FDA had *not* authorised the compound. For example, sirolimus was authorised for preventing organ rejection, and competitors subsequently conducted trials with sirolimus to treat pancreatic cancer.

Whether a trial was aimed at treating a condition that the FDA had already authorised was determined by consulting the World Health Organization’s International Classification of Disease version 11 (ICD-11).⁷¹ The process consisted of three steps. First, the authorised indications for each drug were mapped onto ICD-11 categories via the ICD-11 search function.⁷² Several originators added new indications to their drugs over time (see Table 1). Thus, each indication and corresponding ICD-11 category were dated. Second, the conditions treated in each trial were mapped onto an ICD-11 category. Third, the ICD-11 categories from the first two steps were compared. Clinical trials were labelled as SC trials if the two ICD-11 categories matched, which included situations where the trial category fell

⁶⁹ Liddicoat et al. (2021b), p. 111.

⁷⁰ *Ibid.*, p. 113–114.

⁷¹ World Health Organization n.d., International Statistical Classification of Diseases and Related Health Problems at <https://www.who.int/classifications/icd/en/> (accessed 24 August 2021).

⁷² The authorised indications were obtained from U.S. Food and Drug Administration n.d., Drugs@FDA: FDA-Approved Drugs at <https://www.accessdata.fda.gov/scripts/cder/daf/> (accessed 25 August 2021). Finding the indications on this website is a superior method than using the Orange Book; a previous study used the Orange Book but did *not* identify all the new indications: Sahragardjoonegani et al. (2021). For example, Sahragardjoonegani et al. identified one new indication for celecoxib (treatment of ankylosing spondylitis) after the two initially authorised indications, but this method identified five (four of these are recorded in Table 1 but one, juvenile rheumatoid arthritis, is excluded from the table because it is a paediatric disease).

into a subtype of the authorised category. For example, celecoxib was authorised for relief of the signs and symptoms of osteoarthritis. This indication mapped on to the category “FA0” in ICD-11, titled “osteoarthritis”. FA0 includes seven sub-types of osteoarthritis, including osteoarthritis in specific body parts, such as the hip. Consequently, when a trial treated hip osteoarthritis, it was classified as an SC trial. If the two categories did not match, the trial was labelled as an NC trial; for example, when celecoxib was trialled for amyotrophic lateral sclerosis.

Three authorised indications did not map onto the ICD-11 and, therefore, this study developed its own categorisation system. Ropivacaine was authorised for anaesthesia prior to surgery, and dexmedetomidine was authorised for two indications: first, for sedation of intubated and mechanically ventilated patients in intensive care and, second, for sedation of non-intubated patients prior to or during surgery. Because anaesthesia and sedation are omitted in the ICD-11,⁷³ this study’s categorisation system for these drugs was as follows. Trials that investigated ropivacaine for insensitivity to pain before surgery were classified as SC trials and all other trials were classified as NC trials. For dexmedetomidine’s first indication, trials that investigated reducing agitation or irritability of intubated and mechanically ventilated patients in intensive care were labelled as SC trials, whilst all other trials were labelled as NC trials. And for dexmedetomidine’s second indication, trials that investigated reducing agitation or irritability prior to or during surgery were labelled as SC trials, whilst all others were labelled as NC trials.

3.5 Study Limitations

One limitation in this study is the relatively small number of generic drugs, 15. The authors initially expected a larger number based on the number of generics listed in the FDA’s 2014 list of first generics (96), but only 15 satisfied the inclusion criteria. Although this study analyses nearly 2,000 clinical trials, the limitation remains that these clinical trials originate from a small sample, which can lead to bias. Thus, it is possible that if the sample size were increased, different results might be observed.

Whilst it is generally true that small sample sizes are a limitation, the small sample is also a strength in this study. This study pioneers the idea of looking at clinical trials to examine research on new uses, and this process requires a nuanced reading of the trials (e.g. for distinguishing between NC and SC trials). The smaller sample size also permits the authors more scope to explore the IP strategies underpinning the compounds that were repositioned by competitors *after* the generics were authorised (discussed below).

Another limitation is that this study focuses on small molecules only. Future studies could consider incorporating biologics. This study omitted biologics because relatively few biosimilars have been authorised to date (as of July 2020, 17 different biosimilars have been authorised in Europe,⁷⁴ and, as of March 2021, nine in the

⁷³ That said, the ICD-11 has entries for anaesthetic and sedation “substances”.

⁷⁴ Troein et al. (2020), pp. 30–31 at <https://www.iqvia.com/library/white-papers/the-impact-of-biosimilar-competition-in-europe> (accessed 2 June 2022).

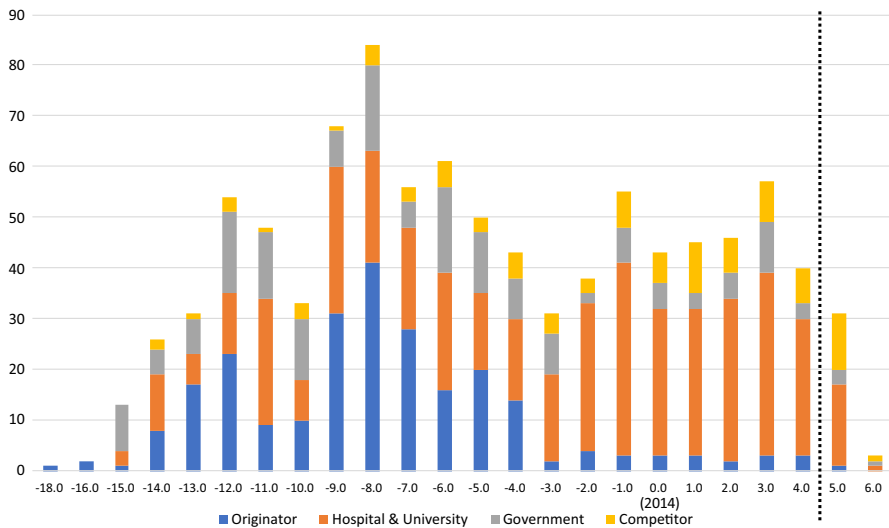


Fig. 1 All clinical trials over time grouped by sponsor type, showing two waves of clinical trials that roughly align with the exclusivity period and the generic period. Years after the dotted vertical line are underestimates

US).⁷⁵ Consequently, researchers should consider how many biosimilars are available and how long they have been on the market before they begin.

4 Results

This study examines the number of clinical trials over time to assess repositioning activity after generics were first authorised for 15 compounds. The study found 959 NC trials were started between when the drugs were initially authorised and 30 March 2020, of which 688 were phase II and 271 were phase III. The method also generates information on new authorisations after generic entry. Two drugs were repositioned in this study after generic entry, and further detail on these drugs can be found in the policy implications section.

4.1 By Various Categories

Figures 1, 2, 3 and 4 group clinical trial data in different ways but also share common features. The x-axes show the number of trials, and the y-axes show time in yearly increments but are organised in a slightly unusual format: each year is calculated from the day the generics were authorised, which is recorded as year “0”. This format means that trials in year 0 began sometime in the 365 days after the generics were authorised in 2014. Likewise, trials in year -1 were conducted in the

⁷⁵ Drugs.com n.d. How Many Biosimilars have been Approved in the United States at <https://www.drugs.com/medical-answers/many-biosimilars-approved-united-states-3463281/> (accessed 25 August 2021).

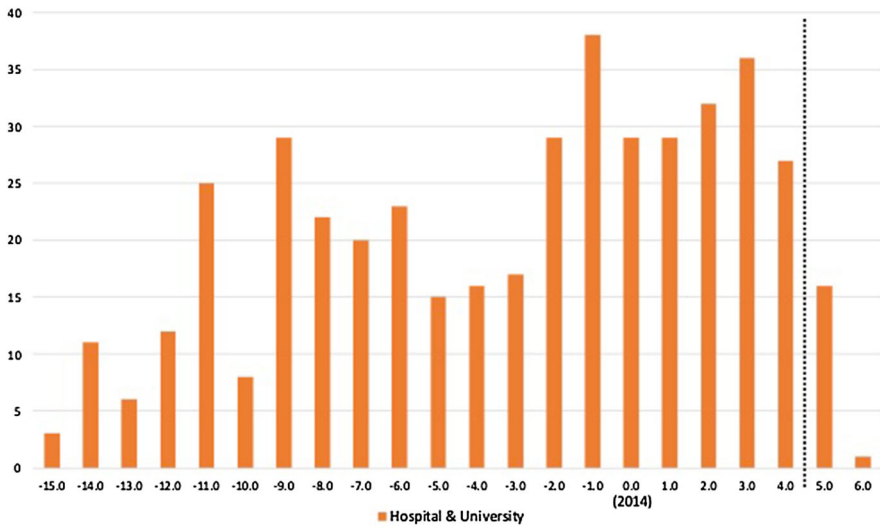


Fig. 2 Hospital and university trials over time. Years after the dotted vertical line are underestimates

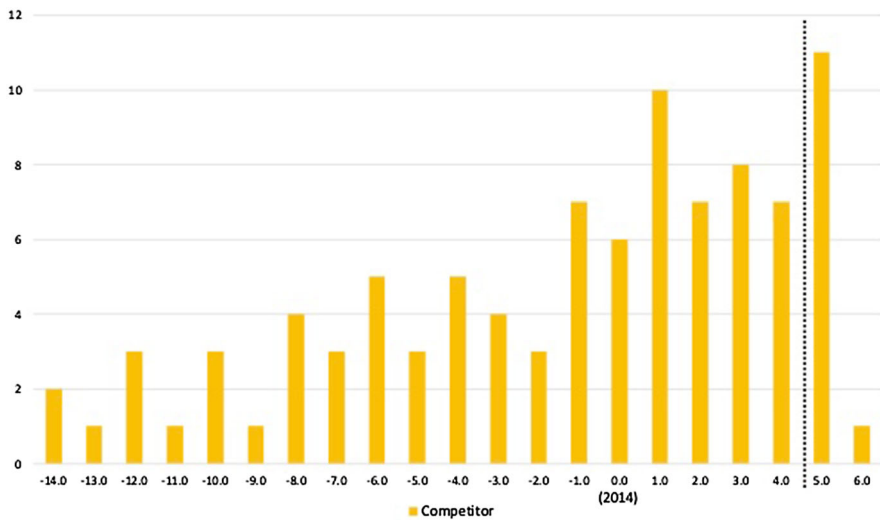


Fig. 3 Competitor trials over time. Years after the dotted vertical line are underestimates

365 days *before* the generic authorisations. This format allows the data for all the drugs to be presented on the same figures, even though they were all authorised on different days. A reminder that year 0 equates to sometime 2014 is recorded in the figures.

Figure 1 shows the number of clinical trials over time grouped by sponsor. Overall, the figure shows that trials occurred in two waves that roughly align with the exclusivity and generic periods. Figure 1 shows that the number of trials during

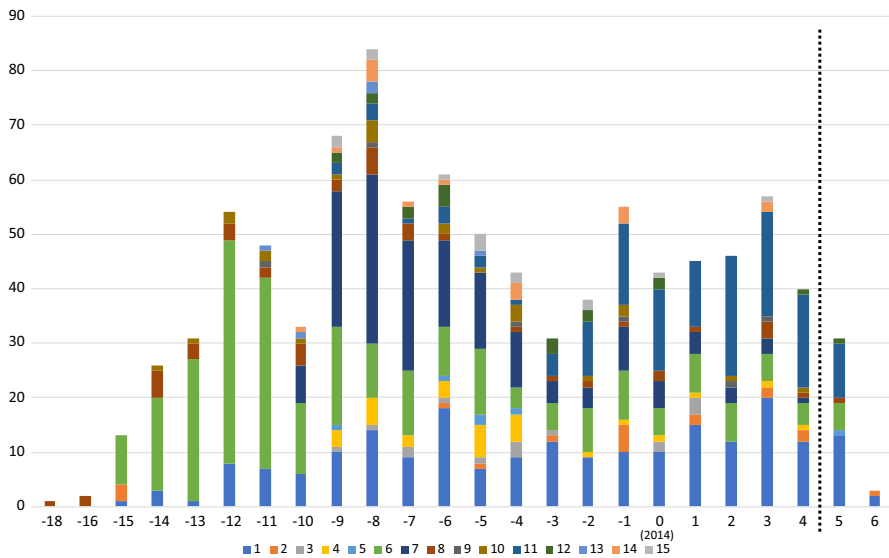


Fig. 4 All clinical trials over time grouped by drug. The drug number refers to the numbers in Table 1. Years after the dotted vertical line are underestimates

the exclusivity period peak at year -8 then drop to a low point at year -3. The second wave then begins two years before the generic period and peaks in year 3. The number of trials appears to significantly decrease in years 5 and 6. However, this appearance is due to two evidence biases. First, the clinical trial data were downloaded from Trialrove on 31 March 2020, and only two of the compounds were authorised before 31 March 2014, which means that only two compounds had been authorised long enough for organisations to begin any trials in year 6. Second, an analyst at Trialrove stated that there is a lag between clinical trials beginning and them being recorded in the database, with information (e.g. trial start dates) sometimes being added months or years *after* the trials begin. For this reason, the data in this study are underestimates beyond year 4. A dotted line is added to Figs. 1, 2, 3 and 4 to remind readers of this uncertainty. Future studies could explore whether the number of trials wanes after year 4.

The sponsors during the two waves are different. In the first wave (year -18 to -3), originators conduct the most trials (223/601 trials, 37%), closely followed by hospitals and universities (207/601 trials, 34%). Governments also sponsor a moderate number of trials (136/601, 23%). During the second wave, however, hospitals and universities conduct most of the trials (237/358, 66%), followed by competitors (60/358, 17%), governments (39/358, 11%) and originators (22/358, 6%).

The second wave is unpredicted by the literature. Indeed, no one comments that competitors or hospitals and universities would *increase* their trial activity. These increases are more visible in Figs. 2 and 3. The second wave is also prolific. Figure 1 shows 246 trials between years -1 and 3 and 319 trials between years -9 and

-5. In other words, Fig. 1 shows that the most prolific period of the second wave contains 77% of the trials during the most prolific period of the first wave. Hospitals and universities also conducted *more* trials during the second wave (164) than originators did during the first (136).

The stark change in originator activity shows that originators effectively stop conducting clinical trials three years before generic entry. On the other hand, Fig. 1 shows that hospitals and universities, as well as competitors, increase their activity *before* generics are authorised. Different reasons likely explain these increases in activity by competitors and hospitals and universities. Competitors are probably anticipating the expiry of patent protection and are exploring whether they could create a market product that uses the drugs.

In comparison, the increase in hospital and university trials is likely due to the availability of cheaper, generic versions of the compounds. Sometimes there is a gap between the authorisation of generics and their availability on the market, but, in this study, 60% of the generics were on the US market within six months of authorisation.⁷⁶ Even if generics are not yet widely marketed, the authorisation permits the generic companies to sell batches of the drug directly to trial sponsors. Patents may still protect the compounds during this period, but the use of patented drugs in experimental clinical trials is typically exempt from patent infringement.⁷⁷

One might argue that the increase in hospital and university trials *before* generic authorisation (i.e. in years -2 and -1) cannot be due to generics. However, originators sometimes lower their prices before the generics are marketed.⁷⁸ Moreover, this study includes clinical trials from all over the world, and it is likely that generics were authorised in other countries one or two years *before* they were authorised in the US (e.g. generics celecoxib and valsartan were authorised in the UK in 2013).⁷⁹

⁷⁶ U.S. Food and Drug Administration 2021, Paragraph IV Patent Certifications at <https://www.fda.gov/media/133240/download> (accessed 25 August 2021). Marketing dates not recorded in this document were obtained from generic organisations' websites. Two colleagues suggested reanalysing the data based on marketing dates (instead of authorisation dates). However, this analysis would omit (i) trials that are conducted using generics obtained directly from the supplier but are not yet marketed more widely and (ii) trials that were conducted using originators' products that are cheaper in anticipation of the generics. These two issues are compounded by the fact two drugs in this study were marketed in 2016 and another two in 2019. These marketing dates mean that clinical trials for these drugs could only be observed for a few years in this study. Consequently, if a market date-based analysis was to be conducted, another study should be conducted that is designed to have the marketing dates all in the same year.

⁷⁷ See, World Intellectual Property Organization (2022), Questionnaire on Exceptions and Limitations to Patent Rights at <https://www.wipo.int/scp/en/exceptions> (accessed 2 June 2022).

⁷⁸ Organisation for Economic Co-operation and Development (2014) Summary Record of the Discussion on Competition and Generic Pharmaceuticals at [https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DAF/COMP/M\(2014\)2/ANN3/FINAL&doclanguage=en](https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=DAF/COMP/M(2014)2/ANN3/FINAL&doclanguage=en) (accessed 2 June 2022), p. 11.

⁷⁹ See, Medicines and Healthcare Products Regulatory Agency (2013a), b, Marketing Authorisations Granted in February 2013 at https://webarchive.nationalarchives.gov.uk/ukgwa/20150121211141mp_/http://www.mhra.gov.uk/home/groups/l-reg/documents/licensing/con249655.pdf (accessed 23 December 2021), p. 3; Medicines and Healthcare Products Regulatory Agency (2013a), b, Market Authorisation Granted in October 2013 at https://webarchive.nationalarchives.gov.uk/ukgwa/20150115225809mp_/http://www.mhra.gov.uk/home/groups/l-reg/documents/licensing/con341247.pdf (accessed 23 December 2021).

Figure 4 shows clinical trials over time grouped by compound. The figure shows that the number of trials varies markedly between the drugs. Several drugs have relatively large numbers of trials (e.g. #1 sirolimus has 208 trials and #6 celecoxib has 261). Whilst other drugs have relatively few (e.g. #5 atazanavir sulphate has 6 trials and #13 frovatriptan succinate has 5). Indeed, the drugs with few trials are barely visible in Fig. 4. The variation in trials per drug affects how Figs. 1, 2 and 3 are interpreted because the variation raises the possibility that outlier drugs with large number of trials skew the data. For example, the outlier drugs could create the false impression that trials continue for *all* drugs in the generic period, when trials continue for only a handful. This result reinforces the need to analyse the data on an individual drug level.

4.2 Individual Drug Analyses

Table 2 compares the average number of trials per year for each drug during the exclusivity and generic periods. Each drug is classified according to the previously explained typology (lower, active, higher or unclassified), which is summarised in the bottom left corner of the table. The comparison is drawn twice between two different cohorts of sponsors, first between all organisations, and second between commercial organisations only. Summaries of the comparisons are located at the bottom of the table.

The two comparisons use slightly different time definitions for the exclusivity and generic periods. In the first comparison (between all organisations), the exclusivity period runs from years -18 to -3 and the generic period runs from -2 to 6. These time periods reflect the increase in hospital and university trials, which are likely due to the availability of cheaper generics. In the second comparison (between commercial organisations), the exclusivity period runs from years -18 to -2 and the generic period from -1 to 6. These time periods reflect the increase in competitor activity, which is likely due to the exclusivity period ending. In each comparison, the time periods were selected to reflect the influence of generic drugs more accurately on clinical trial activity.

The summary of the first comparison in Table 2, which includes trials by all organisations, shows that three drugs are categorised as having lower activity, nine are categorised as active and three as higher. Or, put another way, 12 of 15 drugs (80%) have an active or higher number of clinical trials per year during the generic period compared to the exclusivity period. This result means that most drugs have an active or higher number of trials after generic authorisation, if trials sponsored by all organisations are counted.

The summary of the second comparison in Table 2, which includes commercial trials only, shows that six drugs are categorised as having lower activity, two as active, three as higher and four drugs as unclassified. Or, put another way, about half the drugs have lower activity (6 of 11, 55%) and half (5 of 11, 45%) have an active or higher number.

Table 2 Summary of two comparisons exploring the number of trials per year during the exclusivity period (EP) and the generic period (GP)

# Drug name (INN)	Comparison 1: All organisations' trials			Comparison 2: All commercial trials		
	<u>Exclusivity</u>	<u>Generic</u>	Classification	<u>Exclusivity</u>	<u>Generic</u>	Classification
	Period	Period		Period	Period	
1 Sirolimus	8.52	12.52	Active	1.58	3.32	Higher
2 Rifabutin	0.47	1.97	Higher	0.07	0.85	Higher
3 Solifenacin succinate	1.36	0.83	Active	0.84	0.71	Active
4 Omega-3-acid ethyl ester	3.24	1.00	Lower	2.26	0.43	Lower
5 Atazanavir sulphate	0.56	0.17	Lower	0.10	0.00	Unclassified
6 Celecoxib	15.72	8.58	Active	4.99	1.76	Lower
7 Erlotinib	17.31	4.83	Lower	10.39	1.18	Lower
8 Valsartan	2.13	1.74	Active	1.21	0.44	Lower
9 Ropivacaine	0.24	0.53	Higher	0.00	0.00	Unclassified
10 Bexarotene	1.43	0.89	Active	0.81	0.45	Active
11 Dexmedetomidine	1.26	21.43	Higher	0.22	1.52	Higher
12 Entecavir	1.75	1.07	Active	0.12	0.00	Unclassified
13 Frovatriptan succinate	0.46	0.89	Active	0.34	0.00	Unclassified
14 Daptomycin	1.02	0.72	Active	0.59	0.00	Lower
15 Bimatoprost	0.85	0.55	Active	0.71	0.16	Lower
	Summary			Summary		
Lower, GP ≤50% EP	Lower			Lower		
Active, GP >50% and <200% EP	Active			Active		
Higher, GP ≥200% EP	Higher			Higher		
Unclassified, ≤1 trial every 2 years	Unclassified			Unclassified		
	3			6		
	9			2		
	3			3		
	0			4		
	15			15		

5 Policy Implications

5.1 Answering the Research Questions

To recap, question 1 asked how the number of clinical trials varies from initial authorisation until five years after generics are authorised, and question 2 asked whether clinical trials significantly slow or stop after generics are authorised. Figure 1 shows that there are two waves of clinical trials and that the waves roughly align with the exclusivity and generic periods. Figure 1 also shows that: (i) the total number of trials conducted during the most prolific five years of the generic period equates to 77% of the trials during the most prolific five years of the exclusivity period; and (ii) that hospitals and universities during the most prolific years of the generic period conduct *more* trials than the originators did during the most prolific years of the exclusivity period. Clearly, the number of trials during the generic period shows that trials do *not* stop when generics are authorised. If the downwards trend of trials in years -5 to -3 had continued, then trial activity could accurately be described as significantly slowing. However, this trend does *not* continue. Instead, the number of trials during the second wave are comparable though slightly less the number during the exclusivity period.

Table 2 provides another perspective on whether clinical trials significantly slow or stop after generic authorisation. Table 2 analyses each drug individually and uses the four-group typology to classify them based on the average number of trials per year during the generic period compared to the exclusivity period. If trials by all organisations are included in the comparison, 80% of drugs have an active or higher number of clinical trials during the generic period.

Question 3 asked who is sponsoring the trials. Figures 1, 2 and 3 show that there is a change in who sponsors trials and that this change occurs with the second wave. Years -18 to -3 mainly consist of trials sponsored by originators (37%) as well as hospitals and universities (34%), whereas years -2 to 6 overwhelmingly consist of trials conducted by hospitals and universities (66%). Competitors were the second most frequent sponsor of trials during the generic period, but they sponsored markedly fewer trials (17%).

Although it is common knowledge that hospitals and universities conduct trials to reposition drugs, to date the *scale* of this activity has been unrecognised.⁸⁰ Two reasons potentially explain why relatively large numbers of phase II and III hospital and university trials have gone unnoticed. First, much repositioning commentary concerns off-label use, which is, by definition, *not* brought to the wider-public's attention via labels on drug packaging or authorisation applications. The large number of hospital and university trials – both before and after generic authorisation – indicates many investigators are interested in new uses and, once published, doctors could draw on the data to inform their practice. Unfortunately, this study does not provide insight into whether the investigators were interested in authorisations or only off-label uses. Given the rarity of hospital and university sponsorship of new drug applications, however, the latter may be more likely. Future studies should address this question, as it would shed light on motivations in this area of medical innovation. The second reason that the scale of hospital and university trials has gone unrecognised is decentralisation. Vast numbers of hospitals and universities are distributed across the world, which means the total number is hard to see unless all the trials are collated.

Table 2 provides another perspective on who is conducting the clinical trials. The second comparison concentrates on commercial interests and shows that around half of drugs (between 45%) have an active or higher number of trials during the generic period. These comparisons show that competitors conduct a relatively large number of trials during the generic period compared to originators.

5.2 Do the Results Indicate that Greater Incentives for Commercial Developers Should Be Implemented?

The situation is more complex than it first appears. The results show a higher-than-expected number of repositioning trials, which appears to undermine the argument that more incentives are required. Yet, strengthened incentives *might* still boost

⁸⁰ See Wortzel et al. (2020), p. 10, but the analysis does not focus on trials for repositioning; Pantziarka et al. (2018), pp. 3–4, but the analysis focuses only on phase III trials and drugs authorised for non-cancer indications with potential as cancer treatments.

commercial activity: 55% of drugs have lower trial activity by commercial organisations and the number of hospital and university trials indicates more authorisations for new uses possibly could be pursued. But critical questions are how much more commercial repositioning could be incentivised and at what cost? Commentators to date have ignored or underappreciated existing incentives, and strengthened incentives may only marginally increase commercial repositioning.

One way to increase commercial repositioning is to stop cross-label use by altering prescribing practices. One suggested solution is based on countries implementing software that all physicians and pharmacists use. Physicians would enter information on diagnoses in the software, pharmacists would see the diagnoses when they dispense drugs, and the software would provide details of whether a specific drug should be dispensed due to a patent. The software would also record which drugs pharmacists dispense and, therefore, would show when a pharmacist knowingly dispenses a drug for patented use. The idea is that pharmaceutical companies would have access to the data in the software and could more easily enforce their patents.⁸¹

This software-based solution depends on countries developing and mandating use of the software and on pharmacists being liable for infringement, a proposition that is uncertain in some countries such as the UK,⁸² and one that many find unpalatable.⁸³ It also would require that the software be constantly updated, that physicians and pharmacists be compelled to use the software, and that various players engage in time-intensive oversight, including interpretation of patent claims.⁸⁴ Most significantly, stronger patent rights would increase the costs of pre-existing off-label use, a change that has met with criticism in the past.⁸⁵ Thus, the solution has a list of costs and it remains unsure how successful it would be, especially because it relies on pharmacist liability and requires many countries to implement the software.

Another suggested way to increase repositioning is by lengthening regulatory protection.⁸⁶ However, a recent paper shows that the introduction of the extra year of exclusivity in Europe for repositioning (i.e. extending market protection from 10 to 11 years) failed to increase repositioning,⁸⁷ a result that has several

⁸¹ Roin (2013). Roin also presents an option where pharmaceutical companies do not sue pharmacists. Instead, they “bill insurers directly for the sale”; however, it is unclear how this mechanism would work, and the author provides little detail, *see*, p. 62. A similar solution, albeit with less detail, was described earlier, *see*, Cordery (2013), p. 58; Breckenridge and Jacob (2019), p. 2.

⁸² *Warner-Lambert Co LLC v Generics (UK) Ltd* [2019] 3 All ER 95, at [88], [135], [186] and [197]. However, it should be acknowledged that these statements were made in obiter and how they apply to other types of second medical use claims (*i.e.* EPC 2000 claims) remains unresolved.

⁸³ *See e.g.*, Bostyn (2016), pp. 189–190; Liddicoat (2015), p. 188.

⁸⁴ Another problem here is if the new use attracted market protection but is not protected by a patent, then the drug developer has no enforceable right against pharmacists. Market protection only stops the European Medicines Agency from authorising a generic, it does not provide rights against individuals, *see*, Lietzan (2018), p. 207. Lietzan also suggests an alternative way to stop cross-label use, however, this potential solution is designed for the peculiarities of US pharmaceutical regulation and has limited application outside the US, *see*, 196–209.

⁸⁵ Guglielmo (2021), pp. 287–288.

⁸⁶ Pushpakom et al. (2018), pp. 51–2, 56; Cordery and Willis (2017), pp. 28–29.

⁸⁷ Liddicoat et al. (2021a), pp. 839–844.

explanations,⁸⁸ including the fact that distant revenue streams must be discounted to present value when investment decisions are made, dramatically reducing the value of such extended exclusivities.⁸⁹ Possibly, a lengthened exclusivity would be effective if coupled with stopping or limiting cross-label use. But the plausibility of the latter remains unclear, especially given that ideas to stop cross-label use might not be effective.

The question of whether strengthening incentives would increase commercial repositioning in a cost-effective manner requires further research. This study provides a benchmark for that assessment by describing the number of trials before and after generic authorisation. Future studies could explore this issue by, for example, surveying pharmaceutical companies about how frequently they abstain from developing a new use due to insufficient IP and what would rectify the situation. Reform should seldom be attempted without rigorous evidence, and the higher-than-expected number of repositioning trials run by commercial entities indicates that we do not yet understand this area well enough.

This study reveals two additional considerations regarding greater incentives for commercial trials. First, attempting to strengthen incentives for drug repurposing by extending exclusivity periods could have a net negative impact if it delays the large volume of hospital and university trials that this study shows occur after (and immediately before) generic authorisation. Second, the focus on incentivising commercial trials might be misplaced. Given that hospitals and universities are already conducting trials for new uses, a better strategy might be to pursue authorisations for these new uses through recently established government repositioning programmes. These trials show that these institutes have expertise in the drugs and medical conditions, as well as experience running trials that examine drug efficacy. Thus, continuing to develop the drugs at the hospitals and universities that run the trials or at least in collaboration with them might be more efficient and cost effective.

5.3 Can Society Capitalise on University and Hospital Trials?

An alternative to strengthening incentives is to support and capitalise on the large volume of hospital and university trials. Several governments, primarily American and European, have repositioning programs that could become useful vehicles to achieve this in an efficient, cost-effective manner. In the US, there are several different initiatives, including the MODERN Labelling Act where the FDA has authority to extend indications where sufficient data already exist for a new use.⁹⁰

⁸⁸ *Ibid* 844–845.

⁸⁹ Darrow and Kesselheim (2020), p. 2.

⁹⁰ MODERN Labelling Act 2020, § 2. A question arises: if the drug is already widely used off-label, then will the costs of updating the label outweigh the gains of having the use authorised? For example, *see* Kesselheim and Solomon (2010), p. 2045. This question is beyond the scope of this paper and should be pursued in future research.

Another US initiative provides guidance and scientific assistance on early-stage trials,⁹¹ and a third initiative is focussing on identifying possible new uses by analysing electronic health records.⁹² However, none of these initiatives presently aims to obtain authorisations.⁹³

In contrast, the English and EU programmes aim to obtain authorisations for new uses of generic compounds, and both plan to conduct clinical trials. The English programme aims to conduct trials itself after crowdsourcing new uses from academics and medical practitioners.⁹⁴ The EU programme operates differently: it aims to recruit academics and other experts from not-for-profit organisations into the programme.⁹⁵ The programme will provide the experts with advice and access to its network, but the experts will have to run the trials.⁹⁶

Both programmes are interested in new uses that can be developed cost-effectively and have clinical impact.⁹⁷ Both are also motivated by the common off-label use of some drugs. Off-label use motivates the programmes because not all clinicians prescribe drugs off-label and, therefore, some patients are denied promising though often unproven treatments.⁹⁸ Clinicians may refrain from off-label use because of concerns about the possibility that they (and their employers) could be liable for misusing the drug⁹⁹ or that the cost of the drug would not be reimbursed.¹⁰⁰

⁹¹ National Center for Advancing Translational Sciences (2021), About New Therapeutic Uses at <https://ncats.nih.gov/ntu/about> (accessed 3 May 2022).

⁹² Critical Path Institute n.d., CURE Drug Repurposing Collaboratory at <https://c-path.org/programs/cdr/> (last visited 3 May 2022).

⁹³ See e.g. Breckenridge and Jacob (2019), p. 2; Oprea et al. (2011), p. 62.

⁹⁴ NHS England n.d., Repurposing Medicines in the NHS in England at <https://www.england.nhs.uk/medicines-2/medicines-repurposing-programme/> (accessed January 2022).

⁹⁵ European Commission Expert Group on Safe and Timely Access to Medicines for Patients n.d., Repurposing of Medicines at https://ec.europa.eu/health/medicinal-products/pharmaceutical-committee-veterinary-pharmaceutical-committee-and-expert-groups/commission-expert-group-safe-and-timely-access-medicines-patients-stamp_en (accessed 4 June 2022).

⁹⁶ *Ibid.*

⁹⁷ Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021), pp. 5–6; European Commission Expert Group on Safe and Timely Access to Medicines for Patients 2019, Draft – Proposal for a Framework to Support Not-for-profit Organisations in Drug Repurposing at https://ec.europa.eu/health/sites/default/files/files/committee/stamp/stamp_11_47_2_en.pdf (accessed 25 August 2021), p. 2.

⁹⁸ Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021), pp. 5–6; European Commission Expert Group on Safe and Timely Access to Medicines for Patients 2016, Repurposing of Established Medicines/Active Substances at https://ec.europa.eu/health/sites/default/files/files/committee/stamp/2016-03_stamp4/3_repurposing_of_established_medicines_background_paper.pdf (accessed 24 August 2021), pp. 3–4.

⁹⁹ Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021), p.7.

¹⁰⁰ Verbaanderd et al. (2016), p. 544.

While both programmes aim to obtain authorisations for the new uses, neither actually aim to become marketing authorisation holders (MAHs), nor do they aim for academic or other institutes to become MAHs. The English programme explains that it does not plan to become a MAH because it involves various liabilities and responsibilities, such as conducting ongoing safety studies and maintaining manufacturing facilities.¹⁰¹ Instead, both programmes aim to collaborate with existing MAHs that will add the new use to their existing products.¹⁰² The English programme, however, admits that a weakness in their plan is attracting MAHs. The programme states that many MAHs will not be able to recover the costs of obtaining the authorisations due to the cross-label use.¹⁰³ Consequently, the programme is considering a “catalyst” fund to pay MAHs to obtain the authorisations.¹⁰⁴

The programmes are currently in pilot stages, exploring how they will function. Both programmes already rely on input from universities and hospitals. Yet, the data in this study indicate the programmes could see the hospital and university trials as an R&D pipeline, potentially pursuing large numbers of new authorisations and becoming world leaders in the area. Indeed, the programmes could consider new uses *before* off-label use becomes common. However, the idea that hospitals and universities in conjunction with government programmes could lead generic repositioning at scale is untested and involves a paradigm shift from relying on commercial organisations to reposition drugs. Thus, if the idea is to succeed, it will likely need support and at least three key issues would have to be addressed.

5.3.1 Increasing Recruitment

The first issue is increasing recruitment. The recruitment numbers for originator and hospital and university trials were similar for phase II trials.¹⁰⁵ However, the recruitment numbers for phase III trials differed. The median number recruited for phase III trials by originators was 190, whereas hospitals and universities recruited

¹⁰¹ Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021), pp. 9–10.

¹⁰² Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021), pp. 4, 9–10; European Commission Expert Group on Safe and Timely Access to Medicines for Patients 2019, Draft – Proposal for a Framework to Support Not-for-profit Organisations in Drug Repurposing at https://ec.europa.eu/health/sites/default/files/files/committee/stamp/stamp_11_47_2_en.pdf (accessed 25 August 2021), p. 6.

¹⁰³ Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021), p. 9.

¹⁰⁴ Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 24 August 2021), pp. 4, 11.

¹⁰⁵ The median recruitment for originator trials, and hospital and university trials were 35 and 40, respectively.

91. This difference is statistically significant,¹⁰⁶ showing that university and hospital recruitment is often substantially lower. Moreover, 40% of the originator trials were phase III trials, whilst only 30% of university and hospitals trials were phase III. This means that, in general, a lower proportion of hospitals and university trials are phase III and that, when they conduct phase III trials, they recruit fewer patients.

One of the reasons for the lower numbers is that hospitals and university have difficulty recruiting patients from institutions other than their own. This difficulty arises because they do not have ready access to patient records at other institutions. However, this lack of information is set to change; the EU and the UK are in the process of making electronic health records (EHRs) accessible for research.¹⁰⁷ Academic researchers have stated that recruitment based on EHRs could lead to larger trials and “dramatic cost reductions”.¹⁰⁸ In short, EHRs would allow hospitals and universities to inexpensively recruit larger numbers of patients across multiple institutions in larger areas.

Some of the hospital and university trials may already have sufficient patient numbers to show that the new uses have therapeutic effects, and the smaller numbers of patients observed could in some cases reflect smaller overall patient populations for the new use rather than difficulties in recruitment. However, increasing trial sizes could help the programmes distinguish which new uses are therapeutically promising and those that are not.

5.3.2 Improving the Evidential Value of Trials

The second policy issue concerns the evidentiary value of hospital and university trials, in terms of how convincing the data are to regulators. The EU programme recognises that academics conduct clinical trials and that the evidentiary value of these studies could be improved. In response, the EU has begun a programme called “strengthening training of academia in regulatory sciences and supporting regulatory scientific advice” (STARS), to upskill how academics design and conduct clinical trials.¹⁰⁹ The overarching aim is to “improve the direct regulatory impact of results obtained in medical research”.¹¹⁰

Hospital and university trials could probably be improved in various respects. For instance, the use of placebos, comparator drugs, and which biomarkers are used to assess drug effectiveness. The STARS programme and other more modest programmes, such as the UK’s National Institute for Health Research’s method-

¹⁰⁶ Using a Mann-Whitney U Test, the p-value is 0.03 and z-score is 2.12. The test was performing using an online calculator: Social Science Statistics n.d., Mann-Whitney U Test Calculator at <https://www.socscistatistics.com/tests/mannwhitney/default2.aspx> (accessed 25 August 2021).

¹⁰⁷ European Medicines Agency n.d., Big Data at <https://www.ema.europa.eu/en/about-us/how-we-work/big-data#data-protection-section> (accessed 26 August 2021); NHS Digital (2021), General Practice Data for Planning and Research (GPDPR) at <https://digital.nhs.uk/data-and-information/data-collections-and-data-sets/data-collections/general-practice-data-for-planning-and-research> (accessed 26 August 2021).

¹⁰⁸ Nevens et al. (2019), p. 8; Cowie et al. (2017), p. 3.

¹⁰⁹ Starokozhko et al. (2020), p. 283; *see also*, Pantziarka (2017), p. 456.

¹¹⁰ *Ibid.*

ological advice service,¹¹¹ could help improve non-commercial trials. In turn, these improvements would assist the EU and English programmes because any projects would begin from a better evidence base.

5.3.3 Funding and Attracting MAHs: Can IP on Unique Products Help?

Neither the English nor the EU programme generates income. The English programme aims to fund trials and pay MAHs to obtain authorisation with public funds,¹¹² and the EU programme aims for its experts from academic and not-for-profit organisations to fund the trials.¹¹³ The EU programme omits where the experts might obtain funding and the problem of attracting MAHs.¹¹⁴ Perhaps these approaches to financing clinical trials will work for repositioning a subset of drugs, or a small number per year. However, if the programmes were to capitalise on the pipeline of hospital and university trials and reposition large number of drugs, then more funding would likely be needed. Likewise, a way of attracting MAHs without paying them would help reduce costs.

IP on unique products can address these problems. The idea is that repositioning often involves generating a new product, such as a new dose, because the compound must be optimised for the new condition,¹¹⁵ and IP can stop other companies launching the *same* product. The generic version would still be available, but the generic would be a different product (e.g. a different dose) and, therefore, could not be substituted at the pharmacy under cross-label use.¹¹⁶ Thus, developing a unique drug product protected by IP can reduce or stop cross-label use completely, depending on how frequently physicians *prescribe* the generic drug off-label, which might be risky because the different product may be ineffective or even harmful to patients.

The strategies underpinning two drugs repositioned in this study illustrate the IP-and-unique-products strategy. Rifabutin was originally authorised to prevent a bacterial infection in HIV patients. A competitor then repositioned it into a product called Talicia, which is a three-drug fixed combination (with omeprazole and amoxicillin) for the treatment of a different bacterial infection. Generic rifabutin is

¹¹¹ National Institute for Health and Care Research n.d., Access Methodology Advice at <https://www.nihr.ac.uk/researchers/collaborations-services-and-support-for-your-research/find-services-or-support/access-methodology-advice.htm> (accessed 26 August 2021).

¹¹² Medicines Repurposing Programme Board (2021), Opportunities to Repurpose Medicines in the NHS at <https://www.england.nhs.uk/wp-content/uploads/2021/03/B0342-opportunities-to-repurpose-medicines-in-the-nhs-in-england.pdf> (accessed 23 December 2021), pp. 4, 8, 11.

¹¹³ European Commission Expert Group on Safe and Timely Access to Medicines for Patients 2019, Draft – Proposal for a Framework to Support Not-for-profit Organisations in Drug Repurposing at https://ec.europa.eu/health/sites/default/files/files/committee/stamp/stamp_11_47_2_en.pdf (accessed 25 August 2021), pp. 5–6.

¹¹⁴ It is important to note that hospital and academic trials are often cheaper (*see*, Nevens et al. (2019), pp. 5–6), but the funding problem remains.

¹¹⁵ Lee (2012), pp. 226, 230; Arrowsmith and Harrison (2012), pp. 39–41.

¹¹⁶ Darrow, Chong and Kesselheim (2020), pp. 1–2.

authorised as a single 150 mg capsule in the US,¹¹⁷ but Talicia contains only 12.5 mg of rifabutin and is contained in a delayed-release capsule.¹¹⁸ Although it might be possible to separately prescribe the 150 mg immediate-release capsule of rifabutin and its two counterpart ingredients, it would be less convenient for the patient than the Talicia fixed-dose combination product and evidence would likely not be available to support the safety of the much higher dose of rifabutin in combination with omeprazole and amoxicillin. The markedly different dosage and different coating thus present a very different product compared to generic rifabutin, which likely stops much if not all cross-label use.

The developer of Talicia received three years of market exclusivity for the specific indication when it was authorised and, in addition, an extra five years of exclusivity for developing a Qualified Infectious Disease Product that treats a serious or life-threatening infection.¹¹⁹ The extra five years extends the three years of protection, bringing the total market protection to eight years.¹²⁰ The developer has also stated it has patent protection for the product in the US and Europe (and elsewhere) until 2034.¹²¹ Talicia is not authorised in Europe, but if it were authorised, it would receive the standard eight years of data protection and ten years of market protection.

The second repositioned drug in this study is celecoxib, which was originally authorised for osteoarthritis and rheumatoid arthritis. The drug was actually repositioned twice, but only once did it result in a unique product.¹²² The unique product is called Elyxyb and is authorised for migraines.¹²³ Elyxyb is protected by patents and three years of market protection in the US,¹²⁴ and is available in a 25 mg/ml *solution*, whereas generic celecoxib is available in 50, 100, 200 and 400 mg *capsules*.¹²⁵ IP protection together with a different pharmaceutical form (i.e.

¹¹⁷ See U.S. Food & Drug Administration n.d., rugs@FDA: FDA-Approved Drugs at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=090033> (accessed 3 May 2022).

¹¹⁸ *Ibid.*

¹¹⁹ GlobeNewswire (2019), RedHill Biopharma Announces FDA Approval of Talicia for Treatment of *H. pylori* in Adults at <https://www.globenewswire.com/news-release/2019/11/04/1940084/0/en/RedHill-Biopharma-Announces-FDA-Approval-of-Talicia-for-Treatment-of-H-pylori-in-Adults.html> (accessed 3 May 2022).

¹²⁰ 21 U.S.C. § 355f(a). The eight years protection is not recorded in the US Orange Book.

¹²¹ GlobeNewswire (2019), RedHill Biopharma Announces FDA Approval of Talicia for Treatment of *H. pylori* in Adults at <https://www.globenewswire.com/news-release/2019/11/04/1940084/0/en/RedHill-Biopharma-Announces-FDA-Approval-of-Talicia-for-Treatment-of-H-pylori-in-Adults.html> (accessed 3 May 2022).

¹²² U.S. Food & Drug Administration n.d., Drugs@FDA: FDA-Approved Drugs at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process> (accessed 14 December 2021).

¹²³ U.S. Food & Drug Administration n.d., Drugs@FDA: FDA-Approved Drugs at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process> (accessed 14 December 2021).

¹²⁴ U.S. Food & Drug Administration n.d., Patent and Exclusivity for: N212157 at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=212157&Appl_type=N (accessed 26 August 2021).

¹²⁵ U.S. Food & Drug Administration n.d., Drugs@FDA: FDA-Approved Drugs at <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process> (accessed 14 December 2021).

solution vs. capsules) likely helps reduce cross-label use that could otherwise financially stunt Elyxyb.

One challenge with commercialisation strategies that rely on IP is that they often require planning, and some researchers running the hospitals and university trials will not have considered IP. As mentioned, patents are valid only for novel inventions and, therefore, researchers that conduct clinical trials *before* applying for a patent may compromise their ability to obtain patent rights.¹²⁶ However, a recent article shows granted patents for new uses have been increasing over the last decade, with the top applicants being public-sector entities.¹²⁷ Thus, some of the new uses the programmes will consider will likely already be protected by patents. In addition, the programmes might identify dosages or drug combinations that are patentable during clinical development if, for example, they identify unpredicted therapeutic effects.

Besides patents, some IP requires minimal planning. As outlined above, if an organisation does not hold an authorisation for the compound and applies to obtain authorisation for the new use in Europe, it will receive ten years of market protection.¹²⁸ This period is only half the length of a patent but applies from the date the new use is authorised, whereas patent protection runs from the date of patent application filing which may occur five to ten years before the product it covers is authorised.¹²⁹ Thus, ten years of market protection might offer sufficient IP protection when patents are unavailable.

IP protected unique products present two advantages to the programmes. The first advantage is that MAHs will more likely be interested in obtaining the authorisations because the combination of IP and unique products will be more likely to yield a profit. The second is licence royalties: if some repositioning is valuable, the programmes could consider negotiating royalties with MAHs based on the profits expected from the new uses. The programmes might have to share royalties with partners (e.g. the experts in the EU programme),¹³⁰ but some generic repositioning has been lucrative. For example, an American distributor recently agreed to pay almost US\$100 million (approx. £74 million) in milestone and reimbursement payments *in addition* to royalties.¹³¹

¹²⁶ See e.g., 35 U.S.C. § 102; European Patent Convention 1973, Art. 54.

¹²⁷ Aboy M et al. (2021), pp. 1338–1339.

¹²⁸ Directive 2001/83/EC (OJ L 311 p. 67), Arts. 8(3) and 10(1); The Human Medicines Regulation 2012, Regs. 49 and 51.

¹²⁹ Beall, Darrow and Kesselheim (2019), pp. 21–22.

¹³⁰ How much the EU programme could ask for in royalties should probably depend on the role it plays in the repositioning. The roles programme staff will play are currently unclear. If staff have a hands-off approach to the repositioning, then the programme should probably *not* seek any royalties or only ask for funds to cover the scientific advice it provides. Otherwise, it would be eating into the attractiveness of the new uses to MAHs. On the other hand, if staff consistently assist experts in conducting and designing trials (e.g. assisting with recruitment etc.), it should probably request a greater share. Otherwise, the cost of the programme will be too high. Thus, if the EU programme embraces the IP-and-unique-products strategy, it should probably ensure its agreements with the experts reflect the contribution it makes.

¹³¹ Purple Biotech (2020), Kitov Pharma Provides Corporate Update and Reports First Half 2020 Financial Results at <https://purple-biotech.com/Investors/#b2iLibScrollTo1> (accessed 26 August 2021).

The programmes could fund many or perhaps all of their activities on royalties. However, the idea is not that the programmes should aggressively pursue royalties and IP; rather, the programmes should continue to focus on clinical impact and take advantage of unique products when they arise.¹³² Royalties could be used to subsidise the clinically impactful projects that are not lucrative, as not all new uses can generate IP. In other words, unique products protected by IP could be used to synergistically attract more MAHs and reposition more drugs.

6 Conclusion

This study was motivated by leading commentators arguing that there is an innovation gap in generic drug repositioning and that reform is needed to bridge this gap. Breckenridge and Jacob articulate the argument succinctly, stating “that if a generic version of a drug is available, developers have little or no opportunity to recoup their investment in the development of the drug for a new indication.”¹³³ This study examined this gap by analysing clinical trials for compounds that had generics authorised in 2014.

This study aimed to answer three questions: (i) how do the number of clinical trials aimed at repositioning drugs vary from initial authorisation until five years after generic authorisation; (ii) do trials slow or stop when generics are authorised; and (iii) who is conducting the trials. The study found that trials sponsored by originators peaked eight years before the generics were authorised, then decreased to a minimal level as the authorisation of the generics approached. Yet, clinical trials did *not* stop. Instead, generic authorisation initiated a second wave of clinical trials comparable though slightly less than the number of trials per year observed during the most prolific period *before* the generics were authorised.

The second wave of trials was primarily sponsored by hospitals and universities, as well as competitors. Competitors sponsored only a modest percentage of the trials during the generic period, but their activity is marked by a noticeable increase in trial activity and by the fact they obtained authorisations for three new uses. Indeed, almost half (45%) of the drugs in this study have a “higher” or “active” number of commercial clinical trials per year during the generic period compared to the exclusivity period. This activity is much higher than commentators predicted. One might think that competitor clinical trial activity undermines the argument to increase incentives for repositioning, but the situation is more complex. While the data indicate there is room for more commercial trials, it also reveals limitations in our current understanding of how incentives for repositioning operate. Thus, future studies will have to examine whether more robust IP could increase the number of *commercial* trials and at what cost.

Hospitals and universities sponsored the majority of trials during the generic period. This volume of activity raises the prospect that the focus of many commentators on *commercial* clinical trials is misplaced. England and the EU have

¹³² Frail and Barratt (2021), pp. 39–41; Lee (2012), p. 230.

¹³³ Breckenridge and Jacob (2019), p. 2.

recently established programmes focussing on generating authorisations for off-label uses of drugs. This paper proposes that these programmes could capitalise on the hospital and university trials by using them as an R&D pipeline. The programmes could potentially reposition relatively large numbers of drugs, becoming world leaders in repositioning generic drugs. The programmes could track trials for new uses and seek authorisations for them as they emerge. This tactic would also allow the programmes to move from focussing on seeking authorisations for common existing off-label uses to repositioning generic drugs *before* the off-label use becomes common.

This paper also proposes that the English and EU programmes could embrace IP strategies. The focus of the programmes should remain on clinical impact, and the programmes should not aggressively patent everything they do. However, some repositioning will be eligible for IP protection and result in unique market products. Unique products protected by IP are more likely to be attractive to MAHs, overcoming the concern that MAHs will not want to obtain authorisations for the programmes' new uses. Moreover, if the programmes generate valuable IP, they will be able to negotiate royalties that they could invest back into repositioning. Thus, IP strategies could synergistically help attract MAHs and reposition more drugs, which is the very reason the programmes exist.

This study analysed nearly 1,000 NC clinical trials, but these trials originate from a relatively small sample size of 15 drugs. The findings in this paper should be confirmed in a more extensive study. Nevertheless, the two primary implications from this study can be implemented now. That is, the ideas of examining whether increased incentives will cost-effectively increase commercial repositioning and of the English and EU programmes embracing the IP-and-unique-product strategy to reposition more drugs. Both make sense, even if a more extensive study has slightly different findings. However, if this study's results are confirmed, both implications could be critical to creating the most efficient repositioning system that builds on existing resources and expertise.

Declarations

Conflict of Interest The authors declare they have no competing financial or non-financial interests that are directly or indirectly related to the work submitted for publication.

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