

Incentivising Pharmaceutical Off-Patent Innovation in the EU Recommendations to foster the repurposing of off-patent API

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Covid-19 has emphasised the relevance of pharmaceutical off-patent innovation – i.e. finding other uses for off-patent pharmaceuticals – to design new effective treatments. The EU lags behind the USA, although its innovative potential is very broad. It must remove market inefficiency to stimulate innovation in this field. The Centre de Politique Européenne Paris recommends that:

- ▶ The EU should use the UK Repurposing System as a basis for further development as this would support the industry during the marketing authorisation process by providing public money and regulatory assistance.
- ▶ The EU STAMP framework – designed to give non-profit “champions” the opportunity to bring a repurposed off-patent pharmaceutical to the market – should also be able to authorise profit-oriented “champions” from the private sector.
- ▶ For efficiency reasons, a single public-private European Repurposing Platform should be established as the main instrument to stimulate cooperation and coordination among public and private stakeholders for the testing and adoption of off-patent repurposing opportunities.
- ▶ That platform should include a funding programme for common projects, involving both private and – due to the lack of profitability of off-patent pharmaceuticals – public finance, with private investors predominating.
- ▶ The EU should revise its set of market protection measures to include repurposed off-patent pharmaceuticals, notably by extending the “data ownership” provisions applicable to repurposing companies, for newly approved repurposed off-patent pharmaceuticals, from one to four years.
- ▶ The EU should engage in a discussion with Member States on the pricing and reimbursement of repurposed off-patent pharmaceuticals with added value, taking particular account of the Belgian value-added premia for off-patent pharmaceuticals, with the aim of establishing EU guidelines.

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1 Introduction

This cepInput deals with innovation based on off-patent active pharmaceutical¹ ingredients (“APIs”), which involves finding new uses for these APIs, i.e. repurposing² them. Repurposing includes a) repositioning (adding a new indication³ to a pharmaceutical), b) reformulation (adding a new indication by using a change in the dose or mode of administration of a pharmaceutical) and c) recombination of APIs (adding a new indication by pooling off-patent APIs in order to simplify therapies or combine pharmaceuticals with other devices, such as digital devices⁴). Off-patent means the API is no longer protected by intellectual property rights.⁵ This should not be confused with market and regulatory data⁶ exclusivity⁷ which provides market protection to a pharmaceutical and not directly to an API.⁸

The COVID-19 pandemic has highlighted the importance of repurposing existing off-patent APIs in order to find efficient treatment to fight the pandemic. One example is the case of dexamethasone, a pharmaceutical discovered in 1958⁹ and used e.g. for its anti-inflammatory and immunosuppressant API¹⁰. It proved effective in reducing COVID-19 mortality rates by 21%¹¹ during the publicly funded “RECOVERY” trial in the United Kingdom (UK), a large enrolment clinical trial in which many APIs were tested to find an effective treatment for COVID-19.¹² It has since been widely used to successfully fight serious COVID-19 cases, with an estimated one million lives saved since the approval of the new indication.¹³ It is one example – among many¹⁴ – showing the high potential value that off-patent

¹ In this paper, the term “pharmaceutical” always refers to pharmaceutical – chemistry-based – and biopharmaceutical – biology-based – products and industries.

² For the repurposing definitions, see Value Added Medicines Online Summit, [Empowering the Healthcare community by improving existing treatments](#), 02.2021, p. 2.

³ An indication refers to a medical condition which a pharmaceutical is used for either as a treatment, a prevention or diagnosis of the disease. EMA, [indication](#).

⁴ A digital device here is for instance a software improving patients’ adherence to medication by reminding them to take it. IQVIA, [White paper: a Digital Future for Value added medicines](#), 09.2019, p. 2.

⁵ Intellectual property rights only apply to the jurisdiction of the institution granting them. Therefore, when the European Patent Office grants a patent, it only applies to 38 countries, including the European Union’s Member States, Albania, North Macedonia, Iceland, Liechtenstein, Monaco, Norway, San Marino, Serbia, Switzerland and Turkey. World Intellectual Property Organisation, [EPO – Jurisdiction](#).

⁶ Regulatory data correspond to the data needed to apply for marketing authorisation. It mainly includes data from clinical trials. EMA, [ICH guideline M4 \(R4\) on common technical document \(CTD\) for the registration of pharmaceuticals for human use - organisation of CTD, 19.03.2021](#), p. 6.

⁷ Market exclusivity corresponds to the intellectual right of an innovative pharmaceutical company to be the sole company permitted to market a pharmaceutical for which it has been granted exclusivity. Regulatory data exclusivity means other pharmaceutical companies cannot access the clinical data needed to complete marketing authorisation applications related to the pharmaceutical and are thereby prevented from marketing it. Thus, market exclusivity forms part of regulatory data exclusivity. EMA, [Data exclusivity, market protection, orphan and paediatric rewards](#), 26.10.2018, p. 4.

⁸ This cepInput excludes the case of secondary innovation based on on-patent APIs for secondary innovation is already occurring at this stage. According to a 2021 study, the probability of innovating based on on-patent APIs and on-exclusivity pharmaceuticals peaks between 7 and 8 years before protection (patent & exclusivity) expires and then converges to zero 5 years before expiration. Sahragardjoonegani et al., [Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997](#), 01.2021.

⁹ Cambridge Crystallographic Data Centre, [Dexamethasone briefing – its chemistry and history](#), 06.2020.

¹⁰ The American Society of Health-System Pharmacists, [Dexamethasone](#), 31.07.2017.

¹¹ Assistance Publique – Hôpitaux de Paris, [Prise en charge des formes sévères de Covid-19 : une méta-analyse incluant l’étude CAPE-COVID plaide en faveur de la corticothérapie](#), 03.09.2020.

¹² Águas, R., Mahdi, A., Shretta, R. et al., [Potential health and economic impacts of dexamethasone treatment for patients with COVID-19](#). Nat Commun 12, 915 (2021). RECOVERY is an acronym based on “Randomised Evaluation of COVID-19 Therapy”.

¹³ National Health Service, [COVID treatment developed in the NHS saves a million lives](#), 23.03.2021.

¹⁴ For instance, Viagra, a pharmaceutical used against angina, was repurposed to treat erectile dysfunction. Neuberger A, Oraiopoulos N, Drakeman DL. [Renovation as innovation: is repurposing the future of drug discovery research?](#) Drug Discov Today. 2019 Jan;24(1):1-3, p. 1.

repurposing of APIs can have for innovation in treatment. This report looks at why this potential is not being used in a broader and more systematic way and provides an outlook for the future.

This ceplInput first describes and explains the lack of off-patent innovation in the EU (Section 2) before detailing different existing incentives to tackle this issue (Sections 3 and 4) and going on to assess them (Section 5).

2 Lack of off-patent innovation in the EU

Section 2 first describes the current state of innovation in the EU and the EU's shortfall compared to the United States (USA) in terms of off-patent innovation (Section 2.1). It goes on to describe how innovation generally functions in the EU pharmaceutical sector (Section 2.2) and explains why such a system cannot produce off-patent innovation leading to widespread off-label use of pharmaceuticals (Section 2.3).

2.1 Pharmaceutical innovation in the EU and the USA

The pharmaceutical and biotechnology sector is the second most innovation-intensive in the whole economy, with R&D representing almost 10.6% of net sales in the EU in 2016, after software and computer services with 15%.¹⁵ R&D expenditure in the pharmaceutical and biotechnology sector doubled in the EU between 2000 and 2019, going from €17.8 billion to €36.3 billion per year.¹⁶

Nevertheless, this expansion has been accompanied by a relative decline in EU innovation in the global pharmaceutical sector. Between 2014 and 2018, 47% of new treatments originated in the USA, with only 25% coming from the EU and the UK, whereas at the beginning of the 1990s, the situation was reversed: the EU represented about half of pharmaceutical innovation while the US only a quarter.¹⁷ Furthermore, the global R&D investment share in the pharmaceutical sector is also declining in the EU. Spending on pharmaceutical R&D increased by 450% in the EU between 1990 and 2017 but grew by 800% in the USA over the same period.¹⁸

No concrete statistics have yet been established regarding the size of off-patent innovation as a proportion of total innovation in the EU pharmaceutical sector. A few indices do however suggest that the EU is also lagging behind the USA in this regard. In 2019, off-patent repurposed pharmaceuticals represented 4% of global value of pharmaceutical prescriptions, with 70% of this market in the USA and only 13% in the EU.¹⁹ Thus, some European countries such as France, Germany, Italy, Spain and the UK have developed such a market²⁰ but it has declined during the last decade.²¹ This indicates that off-patent innovation is at a very early stage in the EU compared to the USA.²²

¹⁵ European Commission, [EU Industrial R&D Investment Scoreboard, 2016](#), p. 57.

¹⁶ The values are based on data from EFPIA member associations (official figures). European Federation of Pharmaceutical Industries and Associations, [The Pharmaceutical Industry in Figures](#), 2019, p. 3.

¹⁷ European Federation of Pharmaceutical Industries and Associations, [Would the last pharmaceutical investor please turn the lights out](#), 01.03.2020. Figures come from Pharmaintelligence ([Pharmaprojects](#) & [SCRIP](#)), data from March 2019.

¹⁸ Ibid.

¹⁹ IQVIA, [White paper: A digital future for value added medicines](#), 2019, p. 6.

²⁰ The word 'market' refers to value and sales generated by repurposed off-patent pharmaceuticals.

²¹ IQVIA, [White paper: A digital future for value added medicines](#), 2019, p. 6.

²² More precisely, the American regulatory pathway called « Section 505(b)(2) » dedicated to continuous innovation, represented 50% of marketing authorisations in the US between 2013 and 2018. PharmExec.com, [505\(b\)\(2\): a Pathway to Competitiveness through Innovation for Specialty and Generic Companies](#), 04.12.2019.

2.2 Dominant innovation system in the EU pharmaceutical sector

Developing a *de novo* pharmaceutical²³ is very costly. According to industry-data-based estimates, the average R&D costs for a new chemical or biological API reached €1.93 billion in 2014.²⁴ Other sources put the cost at only €1 billion.²⁵ These costs are mainly composed of success costs (7%), failure costs²⁶ (40%) and borrowing costs (53%).²⁷ The very high proportion of borrowing costs is explained by the high failure rate: less than 10% of applications for marketing authorisation²⁸ regarding *de novo* pharmaceuticals are successful.²⁹

R&D costs cover the discovery phase³⁰ and the clinical trials³¹ that are needed for marketing authorisation. On average, for one new-API-based pharmaceutical reaching marketing authorisation, thousands of APIs have been investigated at the beginning of the research process.³² Then, once the API has been discovered, it goes through a process which usually takes on average twelve years before a pharmaceutical reaches the market.³³ Once clinical data from three different phases of clinical trials³⁴ is available, a pharmaceutical company can apply for a marketing authorisation.³⁵

Given the size of R&D costs, the price of a pharmaceutical is a key component in determining the profitability of pharmaceutical companies. Once a pharmaceutical is authorised, its price is set very differently from one Member State to another as pricing and reimbursement falls within their area of competence.³⁶ Due to various protections, such as patents as well as regulatory data and market exclusivity, pharmaceutical companies can protect their price in order to compensate for their R&D costs and make a profit. The price of a *de novo* pharmaceutical in the EU is protected for at least ten years.³⁷ The

²³ A *de novo* pharmaceutical corresponds to a pharmaceutical based on a newly discovered and investigated API.

²⁴ Pre-tax capitalized costs per approval amount to \$2,558 million (2013 dollars) in their study. Taking the average exchange rate between dollar and euro in 2013 (1.3284 dollar for 1 euro), these costs amount to €1.93 billion per pharmaceutical. Joseph A. DiMasi, Henry G. Grabowski, Ronald W. Hansen, [Innovation in the pharmaceutical industry: New estimates of R&D costs](#), *Journal of Health Economics*, Volume 47, 2016, Pages 20-33, highlights.

²⁵ The average high-quality estimate for investment costs amounts to \$1143.3 billion (2018 dollars) in their study. Taking the average exchange rate between dollar and euro in 2018 (1.1811 dollar for 1 euro), these costs amount to €0.97 billion, i.e. about €1 billion. Wouters OJ, McKee M, Luyten J. [Research and Development Costs of New Drugs—Reply](#). *JAMA*. 2020;324(5):518. p. 869.

²⁶ These costs correspond to all the costs invested in pharmaceuticals which had to stop their development and marketing at any stage of the process. Gupta Strategists, [The cost of opportunity: A study on pharmaceutical R&D costs](#), 02.2019, p. 8.

²⁷ Gupta Strategists, [The cost of opportunity: A study on pharmaceutical R&D costs](#), 02.2019, p. 8.

²⁸ A marketing authorisation in the EU is the approval to market a pharmaceutical in one, several or all European Union Member States. EMA, [Marketing authorisation](#).

²⁹ Ashburn, T., Thor, K. [Drug repositioning: identifying and developing new uses for existing drugs](#). *Nat Rev Drug Discov* 3, 673–683 (2004), p. 1.

³⁰ The discovery phase involves screening essays and toxicity testing. Kraljevic S, Stambrook PJ, Pavelic K. [Accelerating drug discovery](#). *EMBO Rep*. 2004;5(9):837-842, Summary.

³¹ Clinical trials are studies intended to discover or verify the effects of one or more investigational pharmaceuticals, i.e. pharmaceuticals which still have not been granted a marketing authorisation. EMA, [Human regulatory](#).

³² Vagelos, [Are Prescription Drug Prices High?](#), *Science*, New Series, Vol. 252, No. 5009 (May 24, 1991), p. 1082.

³³ Kraljevic S, Stambrook PJ, Pavelic K. [Accelerating drug discovery](#). *EMBO Rep*. 2004;5(9):837-842, Summary.

³⁴ Phase I clinical trials study the safety of the tested treatment on volunteer patients, Phase II clinical trials study efficacy and dosing of the treatment, and Phase III clinical trials assess the added value of the innovation and require a large pool of participants. Cancer.org, [types and phases of clinical trials](#), 18.08.2020.

³⁵ The EMA asks for clinical study reports for every phase to be included in the marketing authorisation application. EMA, [ICH guideline M4 \(R4\) on common technical document \(CTD\) for the registration of pharmaceuticals for human use – organisation of CTD, 19.03.2021](#), p. 6.

³⁶ EMA, [The European regulatory system for medicines](#),

³⁷ As mentioned in the introduction, data and market exclusivities apply to pharmaceuticals and not to APIs. In Europe, marketing authorisation automatically grants eight years of data exclusivity (which also includes market exclusivity) and

total exclusivity can be extended to eleven years if, during the first eight years of exclusivity, the innovative pharmaceutical company obtains an authorisation for one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison with existing therapies.³⁸ In reality, the protection of pharmaceuticals is longer than these ten or eleven years of market exclusivity: the European Commission found in 2019 that effective protection amounted to 13 years, down from 15 years in 1996³⁹, e.g. thanks to supplementary protection certificates which protect the API for five more years, adding up to 25 years of API protection, which by extension also protects the pharmaceutical's price and market from competition.⁴⁰

2.3 Specificity of off-patent innovation in the EU

Off-patent innovation does not follow the same rules as those described above. First, repurposing an off-patent API does not entail as much cost as developing a *de novo* pharmaceutical based on a newly discovered API. There is no longer any need for an initial research and discovery phase.⁴¹ Overall, the cost of repurposing an API is generally lower than the development of a new pharmaceutical but still amounts to about 50-60% of the R&D cost for a *de novo* pharmaceutical.⁴²

When it comes to the price of repurposed off-patent pharmaceuticals in the EU, the fact that no market protection is granted for the new indication – except for very specific cases⁴³ – means that nothing prevents a pharmaceutical company from using the repurposed off-patent APIs⁴⁴ with this new indication.⁴⁵ Any company can access the regulatory data used for the market authorisation and perform the repositioning, reformulation or recombination developed by the innovative company. As a result, this quantity of off-patent pharmaceuticals adjusts to demand, prices are as competitive as for generic pharmaceuticals,⁴⁶ and they are treated like generic pharmaceuticals by the regulator. More precisely, generic prices respond to supply but also receive regulation from national authorities. For instance, in France, the discount compared to the price of the original pharmaceutical must be 60% when the generic pharmaceutical makes its market entry.⁴⁷ In Portugal and Italy, this discount is 50%, in Germany

two years of subsequent market exclusivity during which competitors can access regulatory data. EMA, [Data exclusivity, market protection, orphan and paediatric rewards](#), 28.10.2018, p. 5.

³⁸ EMA, [Data exclusivity, market protection, orphan and paediatric rewards](#), 28.10.2018, p. 3.

³⁹ European Commission, [Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe](#), 2021, p. 12.

⁴⁰ *Ibid.*, p. 69.

⁴¹ Hernandez JJ, Prysizlak M, Smith L, Yanchus C, Kurji N, Shahani VM and Molinski SV (2017), [Giving Drugs a Second Chance: Overcoming Regulatory and Financial Hurdles in Repurposing Approved Drugs As Cancer Therapeutics](#). *Front. Oncol.* 7:273. p. 2.

⁴² *Ibid.*, p. 2.

⁴³ See Section 3.1 for more details.

⁴⁴ The Input uses the expression of “repurposed off-patent API” when the repurposed API has still not resulted in a repurposed pharmaceutical, which happens when the repurposing company succeeds in being granted a marketing authorisation for its new indication. In this case, “repurposed off-patent pharmaceutical” is used.

⁴⁵ In Europe, no regulatory protection is provided to off-patent repurposed pharmaceuticals. It is worth noting that this situation is very different in the US where the regulatory pathway « Section 505(b)(2) » grants between three and seven years of market exclusivity. See Section 4.1 for more details. US Food & Drug Administration, [Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity](#), 02.11.2016.

⁴⁶ A generic pharmaceutical is a pharmaceutical that is developed to be the same as a pharmaceutical that has already been authorised. Its authorisation is based on efficacy and safety data from studies on the original pharmaceutical. EMA, [Generic medicine](#).

⁴⁷ European Commission, [External reference pricing of medicinal products: simulation based considerations for cross-country coordination](#), p. 72.

10% (both for the original and generic pharmaceuticals).⁴⁸ Furthermore, generics are generally included in external reference pricing schemes⁴⁹ – which limit price-fixing of generics to a bandwidth based on the prices for the same pharmaceutical abroad. Repurposed off-patent pharmaceutical prices also comply with these discounts.

Off-patent innovation therefore faces two challenges: a) significant costs and long development phase⁵⁰ and b) uncertain price on the markets, in other words: uncertain profits. This results in a lack of incentive to repurpose off-patent APIs for the pharmaceutical sector. Furthermore, the potential reduction of market potential due to clinical trials revealing dangerous side effects is also a disincentive for the industry.⁵¹ Despite this, the lack of incentive results in wide off-label use of pharmaceuticals⁵² in the health sector, especially for tackling unmet needs. Indeed, there is no EU law provision which prevents a pharmaceutical being prescribed for therapeutic indications other than those for which a marketing authorisation has been granted.⁵³ The repurposing of off-patent APIs may contribute to limiting the need for off-label use, hence limiting the risks involved.

3 Ex-ante incentives to tackle the lack of off-patent innovation

To tackle the lack of off-patent innovation in the pharmaceutical sector, incentives may be used in at least four different stages of the repurposing process:

- (1) in the initial stage, by granting more funding for research and development and triggering more cooperation between stakeholders,
- (2) when the innovative organisation chooses its regulatory pathway⁵⁴ for marketing authorisation, by introducing features favourable to quicker patient access and commercialisation,
- (3) when the regulator grants marketing authorisation linked to market protection, by creating a protection favourable to repurposed pharmaceuticals,
- (4) when the price of the repurposed pharmaceutical or the new indication is set, by introducing premiums rewarding the added value of the pharmaceutical.

Section 3 will therefore focus on incentives created by public authorities to target repurposing, which take effect before marketing authorisation – (1) and (2) –, known as ex-ante incentives, while Section

⁴⁸ Nayroles G, Frybourg S, Gabriel S, Kornfeld Å, Antoñanzas-Villar F, Espín J, Jommi C, Martini N, de Pouvourville G, Tolley K, Wasem J, Toumi M. [Unlocking the potential of established products: toward new incentives rewarding innovation in Europe](#). J Mark Access Health Policy. 2017 May 12;5(1):1298190. p. 3.

⁴⁹ Pharmaceutical Pricing and Reimbursement Information, [External Price Referencing \(EPR\)](#).

⁵⁰ Between three and twelve years vs. between five and 15 years for an original pharmaceutical ; see for the first range Hernandez JJ, Prysizlak M, Smith L, Yanchus C, Kurji N, Shahani VM and Molinski SV (2017) [Giving Drugs a Second Chance: Overcoming Regulatory and Financial Hurdles in Repurposing Approved Drugs As Cancer Therapeutics](#). Front. Oncol. 7:273. p. 2., and see for the second range European Commission, [Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe](#), 05.2018 p. 21.

⁵¹ European Commission, [Study on off-label use of medicinal products in the European Union](#), p. 10.

⁵² Off-label use in the health sector involves the use of a medicine for an unapproved indication or in an unapproved age group, dosage, or mode of administration, which is generally necessary to fulfil the individual patient's needs. It is common practice in the health sector for physicians to prescribe pharmaceuticals off-label, especially in clinical areas of high unmet needs, i.e. oncology/haematology, psychiatry and rheumatology. The paediatric and rare disease population is the main target. Off-label use is present both in hospitals and outpatient settings. An increasing demand from patients and physicians to obtain a marketing authorisation for the new use, and the time and costs needed to investigate a new indication, are the main reasons for off-label use. For further details, see European Commission, [Study on off-label use of medicinal products in the European Union](#), p. 10 and p. 15.

⁵³ European Court of Justice, [Laboratoires CTRS vs Commission](#), paragraph 79.

⁵⁴ A regulatory pathway is a procedure set by the regulators that applicants must follow to potentially be granted a marketing authorisation. EMA, [Authorisation of medicines](#).

4 will focus on incentives created by public authorities to target repurposing, which take effect after marketing authorisation – (3) and (4) –, known as ex-post incentives. These two sections consider valuable incentives both inside and outside the EU.

Regarding ex-ante incentives,⁵⁵ the EU is developing a system for off-patent innovation (Section 3.1) and the UK a system for repurposing – not only targeted at off-patent APIs (Section 3.2).

3.1 EU system for off-patent innovation

The EU is developing an innovative public-private framework for repurposing (Section 3.1.1) and has a project for a Repurposing Platform financed by Horizon Europe (Section 3.2.1).

3.1.1 STAMP framework to repurpose off-patent APIs

In 2016, the EU Commission created the “Safe and Timely Access to Medicines for Patients” (“STAMP”) expert group⁵⁶, whose mission, among other things, is to develop innovative pathways to bring repurposed pharmaceuticals to the market. In 2018, the industry proposed an experimental framework⁵⁷ to ease the repurposing of off-patent APIs,⁵⁸ which was adopted by the Pharmaceutical Committee⁵⁹ in 2019. The aim of the framework is to bring new indications on-label⁶⁰ – using existing pharmaceuticals – and to identify how stakeholders collaborate in this context.⁶¹ In other words, the repurposing framework aims to foster the authorisation of an indication for an off-patent API, for which some data have already been generated thanks to its off-label use.⁶²

The scope of the framework – launched in 2021⁶³ – is as follows:⁶⁴ A new indication for a well-established pharmaceutical⁶⁵ has to be identified, as distinct from the current authorised indications, by a

⁵⁵ The frameworks mentioned in Sections 3.1 and 3.2 mostly include ex-ante incentives, and very marginally ex-post incentives. See Section 4 for more details.

⁵⁶ The STAMP expert group is set up to provide advice and expertise to the Commission services in relation to the implementation of the EU Pharmaceutical legislation, as well as programmes and policies in this field. STAMP exchanges views and information about the experience of Member States, examines national initiatives and identifies ways to use more effectively the existing EU regulatory tools with the aim of further improving safe and timely access and availability of pharmaceuticals for patients. It is a working group including representatives from Member States, the European Medicines Agency (EMA) and stakeholders from industry, not-for-profit organisation, patient, healthcare and payer representative organisations. European Union, [Scope, objectives and functioning of the Commission Expert Group on Safe and Timely Access to Medicines for Patients \(“STAMP”\)](#), 06.12.2018, p. 1.

⁵⁷ This framework is a protocol for repurposing, relying on existing legal provisions, to be tested in anticipation of a more definitive framework ex-post. It is more focused on cooperation between stakeholders rather than providing for new regulatory paths to market.

⁵⁸ European Commission, [Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines](#), 2019.

⁵⁹ The Pharmaceutical Committee is an advisory body for the EU Commission. It is a forum where the Commission, Member States, EMA and its other members, such as EEA countries, can interact on policy and implementation issues relating to the pharmaceutical acquis. European Commission, [Pharmaceutical Committee](#), 11.2019, p. 1.

⁶⁰ Using a pharmaceutical on-label means the pharmaceutical is used for the indication, age, group, dosage or mode of administration which was applied for during the marketing authorisation process. Inferred from EMA, [Off-label use](#).

⁶¹ European Commission, [Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines](#), 2019, p. 1.

⁶² *Ibid.*, p. 4.

⁶³ EMA, [Repurposing of authorised medicines: pilot to support not-for-profit organisations and academia](#), 28.10.2021.

⁶⁴ For the entire paragraph: European Medicine Agency, [Repurposing of established substances](#), 25.09.2019, p. 7.

⁶⁵ A well-established pharmaceutical is based on an API which has been used for more than ten years and whose efficacy and safety have been well established. When they are the object of further applications for marketing authorisation, the latter can be based on results from the scientific literature. One year of regulatory data protection is granted in this case (Art. 10(5) of Directive (EC) 2001/83). EMA, [Well-established use](#).

Member State or the EU, in an area where significant public health benefits are likely to be achieved.⁶⁶ The well-established pharmaceutical must be free from any regulatory protections and there should already be supporting evidence that the API is effective in the context of the new indication (real world evidence⁶⁷). Finally, a “champion” – a non-profit organisation⁶⁸ – would assume responsibility for taking all the steps necessary to bring this identified indication on-label. The protocol is as follows.⁶⁹

- (1) the champion identifies a new indication which it wants to put on-label and approaches the European Medicines Agency (EMA) and/or equivalent national authorities to integrate the STAMP framework,⁷⁰
- (2) using identified data sources and/or own data, the champion submits its proposal to enter either an EU or a national pre-existing regulatory pathway to the relevant regulatory authority and arranges a meeting.⁷¹ Other stakeholders (patient groups, clinical investigators, etc.) may attend. It can already contact marketing authorisation holders (MAHs) to get advice regarding clinical data generation and regulatory pathways to marketing authorisation.⁷²
- (3) it seeks scientific advice⁷³ from the regulator who decides whether the well-established pharmaceutical should follow the chosen pathway. If not, the regulator can signpost to different existing regulatory pathways.⁷⁴
- (4) the champion follows the regulator’s recommendations and seeks the appropriate MAH from the private sector to bring the new indication on-label,⁷⁵
- (5) the MAH and the champion collaborate to create relevant data for filing, responses and inspections from the regulator.⁷⁶
- (6) As an incentive, the MAH can either benefit from the orphan designation,⁷⁷ paediatric use marketing authorisation,⁷⁸ or the one-year regulatory data protection for well-established

⁶⁶ European Commission, [Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines](#), 2019, p. 3.

⁶⁷ Clinical evidence gathered through research performed after marketing authorisation of a pharmaceutical. EMA, [Real world evidence – what have we learned recently at EMA ?](#)

⁶⁸ A champion cannot be a private company and cannot be financed by private profit organisations in the pharmaceutical sector, nor can it have concluded any operating agreements with any pharmaceutical company regarding their sponsorship or participation to the specific research project at the time of entry into the framework. It must coordinate or foster research up until the point of full industry engagement. It coordinates the project by engaging all stakeholders of the process (regulator, industry, patient groups, etc.). European Commission, [Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines](#), 2019, p. 3.

⁶⁹ European Commission, [Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines](#), 2019, p. 8.

⁷⁰ *Ibid.*, p. 5.

⁷¹ *Ibid.*, p. 5-6.

⁷² *Ibid.*, p. 6.

⁷³ EMA provides scientific advice to support the timely and sound development of high-quality, effective and safe pharmaceuticals, for the benefit of patients. EMA, [Scientific advice and protocol assistance](#).

⁷⁴ European Commission, [Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines](#), 2019, p. 6.

⁷⁵ *Ibid.*, p. 6.

⁷⁶ *Ibid.*, p. 6.

⁷⁷ Orphan designated pharmaceuticals authorised for marketing in the EU are eligible for ten years’ market exclusivity for the orphan designated indication. EMA, [Applying for orphan designation](#).

⁷⁸ Pharmaceuticals which are authorised for a paediatric use pursuant to a paediatric investigation plan agreed by the EMA are eligible for a separate period of data and marketing protection (8+2 years) for that paediatric indication. EMA, [Paediatric-use marketing authorisation](#).

pharmaceuticals.⁷⁹ Nevertheless, price is fixed according to every Member State's price setting system, depending on the respective national Health Technology Assessment⁸⁰.

3.1.2 Project to create an EU Repurposing Platform

Within its funding programme "Horizon Europe" (2021-2027), the EU is currently organising a tender to grant 50 million euros to create a Repurposing Platform.⁸¹

The tenderers must submit a proposal tackling the following issues: a) developing a new repurposing model attracting worldwide investment to make the EU take a global leadership position in this domain⁸², b) providing for transparent selection mechanisms for prioritising approved and investigational pharmaceuticals,⁸³ c) using innovative ways of repurposing opportunity identifications such as pharmacogenomics,⁸⁴ preclinical in-vitro methods, but also artificial intelligence, d) finding a way to create a functioning cooperation between all EU stakeholders, e) solving the problem of lack of ownership in repurposing projects.⁸⁵ The Repurposing Platform is expected to be established in the coming years.⁸⁶

3.2 UK Repurposing System

The UK Repurposing System is composed of a Repurposing Medicines Programme⁸⁷ establishing a catalyst public fund for repurposing (Section 3.2.1) and a new flexible regulatory pathway (Section 3.2.2).

3.2.1 Medicines Repurposing Programme

The Medicines Repurposing Programme launched in March 2021 aims to minimise the barriers for any "repurposable" pharmaceuticals which could significantly improve patient care and associated outcomes and are likely to fulfil the requirements for funding in the National Health Service ("NHS").⁸⁸ A pilot project has already started⁸⁹.

⁷⁹ A well-established substance is an API which has been used for more than ten years and its efficacy and safety have been well established. When they are the object of further applications for marketing authorisation, the latter can be based on results from the scientific literature. One year of regulatory data protection is granted in this case (Art. 10(5) of Directive (EC) 2001/83). EMA, [Well-established use](#).

⁸⁰ A health technology assessment is the systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences, and aimed mainly at informing decision making regarding health. O'Rourke et al., [The new definition of health technology assessment : A milestone in international collaboration](#), 2020, p. 1.

⁸¹ Funding & tender opportunities of the European Commission, [Building a European innovation platform for the repurposing of medicinal products](#), 22.06.2021.

⁸² The proposal should integrate the scientific, methodological, financial, legal, regulatory, and intellectual property aspects of the repurposing approach. Funding & tender opportunities of the European Commission, [Building a European innovation platform for the repurposing of medicinal products](#), 22.06.2021.

⁸³ An investigational pharmaceutical is a product which has been used in clinical trials but not brought to the market with its initial indication. Repositioning in this case allows for R&D cost compensations. NIH, [Investigational product](#).

⁸⁴ Pharmacogenomics is a field of research that studies how a person's genes affect how they respond to medications. NIH, [Pharmacogenomics](#).

⁸⁵ On 22 July 2021, 27 organisations were looking for partners to deliver a proposal. [Among them](#), research organisations, public entities such as chambers of commerce, software companies, universities and hospitals can be found.

⁸⁶ The tender ends on 22 September 2021.

⁸⁷ This Programme is a roadmap and is not based on any specific legal provision in the UK.

⁸⁸ NHS, [Opportunities to Repurpose Medicines in the NHS in England](#), 02.03.2021, p. 3.

⁸⁹ The Mesenchymal Stem Cell Study for Children with Epidermolysis Bullosa (MissionEB) was the first pilot topic taken through NHS England's National Research Collaboration Programme with NIHR. NHS, [Opportunities to Repurpose Medicines in the NHS in England](#), 02.03.2021, p. 12.

This Repurposing Medicines Programme proceeds as follows:⁹⁰

- (1) new indications are identified by charities and lead clinicians within the Information Observatory⁹¹ of the UK's National Institute for Health Research ("NIHR"). They are not necessarily targeting off-patent APIs.⁹²
- (2) a roadmap is drawn up and a program team is established to coordinate all the involved stakeholders, from the clinical data generation process to the marketing authorisation, under the supervision of British public authorities.⁹³
- (3) a catalyst fund – i.e. where private investors and companies can co-invest – helps finance these processes, the goal being to support two to three new indications per year in 2021 and 2022⁹⁴, then six from 2023 onwards.
- (4) fast-track evidence generation is pursued using either existing or tailor-made regulatory pathways, in collaboration with British public authorities (see Section 3.2.2).⁹⁵ Either pharmaceutical companies or public research centres could take charge of clinical data generation.
- (5) It is expected that any incentives for MAHs to repurpose an API will be delivered in a way that does not impact existing pricing and reimbursement systems, which promote effective competition.⁹⁶

3.2.2 Innovative Licensing⁹⁷ and Access Pathway

This new Repurposing Program has now been completed by a new regulatory pathway, launched on 1 January 2021, which not only addresses repurposing but makes it easier: The Innovative Licensing and Access Pathway ("ILAP").⁹⁸ This pathway aims at accelerating the time to market⁹⁹, to ease patient access to pharmaceuticals by providing a single integrated platform for sustained collaboration between the MHRA, partners and the MAHs.¹⁰⁰ It is open to repurposed off-patent pharmaceuticals, and to both commercial and non-commercial developers of pharmaceuticals.

A pharmaceutical company can obtain an "Innovation Passport" if it addresses a life-threatening or seriously debilitating condition or a significant unmet need. The pathway is also open without clinical trials data supporting the benefits of the pharmaceutical for patients. It can only base its claim on data from valid non-clinical models, i.e. real-world evidence from post-approval studies¹⁰¹, or data inferred

⁹⁰ NHS, [Opportunities to Repurpose Medicines in the NHS in England](#), 02.03.2021, p. 3-4.

⁹¹ Ibid., p. 3.

⁹² Ibid., p. 3.

⁹³ These are the Medicines and Healthcare Regulatory Agency ("MHRA"), the National Institute for Health and Care Excellence ("NICE") and the NIHR.

⁹⁴ The necessary funding for repurposing in these cases is expected to be very small given the fact the NHS estimates the budget to be around £10.5 million yearly to add three indications per year. NHS, [Opportunities to Repurpose Medicines in the NHS in England](#), 02.03.2021, p. 11.

⁹⁵ NHS, [Opportunities to Repurpose Medicines in the NHS in England](#), 02.03.2021, p. 15.

⁹⁶ Ibid., p. 4.

⁹⁷ In the UK, licensing is the process through which pharmaceuticals obtain a marketing authorisation – called a license. British Medical Journal, [The licensing of medicines in the UK](#), 2015.

⁹⁸ For the rest of the sub-section : MHRA, [Innovative Licensing and Access Pathway](#), 30.03.2021.

⁹⁹ The time to market corresponds to the timespan between the beginning of the development of a pharmaceutical and its marketing authorisation.

¹⁰⁰ GOV.UK, [The MHRA Innovative Licensing and Access Pathway is open for business](#), 01.01.2021.

¹⁰¹ These studies are also called pragmatic or practical clinical trials. Tunis et al., [Practical Clinical Trials](#), 2003, p. 1631.

from clinical trials dedicated to another indication. The goal of the Innovation Passport is to create a Target Development Profile for every candidate, resulting in a tailor-made regulatory pathway¹⁰².

4 Ex-post incentives to tackle the lack of off-patent innovation

At EU level, no legal provision foresees incentives based on pricing and reimbursements, or on market protection – except for some specific cases¹⁰³ – for off-patent repurposed pharmaceuticals. Two types of ex-post incentives could motivate the pharmaceutical industry to repurpose off-patent API: incentives linked to reward (pricing, reimbursement policies, prizes, etc.) and market protection, which are complementary. The American system provides for market protection for off-patent pharmaceuticals (Section 4.1) while Belgium provides for a reward-based incentive (Section 4.2).

4.1 Section 505(b)(2) of the US Federal Food, Drug and Cosmetic Act

The US system provides three main regulatory pathways: Section 505(b)(1) for *de novo* pharmaceuticals,¹⁰⁴ Section 505(b)(2) for repurposed off-patent pharmaceuticals,¹⁰⁵ and Section 505(j) for generic pharmaceuticals.¹⁰⁶ In 1984, the USA introduced Section 505(b)(2) to allow for off-patent repurposed pharmaceuticals to benefit from between three and seven years of non-cumulative¹⁰⁷ regulatory data exclusivity.¹⁰⁸ This exclusivity regime grants the following exclusivity according to the characteristics of the pharmaceutical to be approved: three years for repurposed off-patent pharmaceuticals, seven years for repurposed orphan pharmaceuticals, which can also add six months of exclusivity if the pharmaceutical shows a paediatric indication.¹⁰⁹

4.2 Belgian added-value premium for repurposed pharmaceuticals

In Belgium, if a new value-added indication for an off-patent API is found (either repositioning, reformulation or recombination), the insurers grant a premium to the successful pharmaceutical company during the price bargaining process, as long as it does not destabilise healthcare insurance sustainability.¹¹⁰ More precisely, the fiscal impact cannot exceed €2.5 million per year during the three first years of commercialisation and must be less than € 250,000 per patient per year during the three first years.¹¹¹

5 General assessment

The UK's Repurposing System (see Section 3.2) provides for more flexibility than the EU STAMP Framework (see Section 3.1.1) a) because it does not identify ex-ante a "champion" in charge of the

¹⁰² Rational Vaccines, [Rational Vaccines Receives UK MHRA Innovation Passport for RVx201 for the Treatment of Genital Herpes Resulting From Herpes Simplex Type 2 \(HSV-2\) Virus](#), 22.07.2021.

¹⁰³ The EC STAMP framework assumes the use of three incentives to repurpose pharmaceuticals: orphan designation, paediatric formulation marketing authorisation, and one-year regulatory data exclusivity for well-established substances. See 3.1.1 for more details.

¹⁰⁴ United States' Food and Drugs Administration, [Applications covered by section 505\(b\)\(2\)](#).

¹⁰⁵ Ibid.

¹⁰⁶ Ibid.

¹⁰⁷ Non-cumulative means here it is not possible to add new regulatory data or market exclusivity subsequently.

¹⁰⁸ United States' Food and Drugs Administration, [Applications covered by section 505\(b\)\(2\)](#), 24.09.1984.

¹⁰⁹ Longworth et al., [The 505\(b\)\(2\) Drug Approval Pathway: A Potential Solution for the Distressed Generic Pharma Industry in an Increasingly Diluted ANDA](#), 03.2018, table I.

¹¹⁰ Belgian Government, [Arrêté royal fixant les procédures, délais et conditions en matière d'intervention de l'assurance obligatoire soins de santé et indemnités dans le coût des spécialités pharmaceutiques](#), 01.02.2018, p. 56.

¹¹¹ Ibid.

repurposing project (see Section 3.2.1), b) by allowing as valid repurposing opportunities APIs involved in off-label uses that are not necessarily off-patent, c) by allowing for tailor-made regulatory pathways thanks to the Innovative Licensing and Access Pathway (see Section 3.2.2) and its Target Development Profile, as well as the strong involvement of the MHRA, and d) by explicitly allowing non-profit organisations to be MAHs. It also provides for more public support than the EU STAMP framework a) regarding the funding through a catalyst fund financed by the NHS for repurposing opportunities, b) regarding the regulatory data generation process with strong involvement of the MHRA. The UK therefore spends more public resources than the EU to stimulate pharmaceutical off-patent innovation through ex-ante incentives.

The regulatory flexibility regarding repurposing opportunities introduced by the ILAP is well suited to taking account of the specificity of each repurposable off-patent API and the different reasons motivating the stakeholders involved – for physicians it is their treatments, for research centres it is science, for pharmaceutical companies it is profits, etc. – such that each project can design its own roadmap for achieving market authorisation. This flexible regulatory framework could also reduce failure rates – especially if physicians and researchers, who are aware of real-world evidence, collaborate with the pharmaceutical industry – and reduce time to market thanks to tailor-made regulatory pathways. Public funding for repurposing opportunities is also a way to leverage repurposing projects using private investment if expected profits are positive¹¹² and, thus, enhance the pool of repurposed pharmaceuticals for the benefit of both innovation in the private sector and of patients. The EU should therefore use the UK Repurposing System as a basis for further development as this would support the industry during the marketing authorisation process by providing public money and regulatory assistance. For instance, the EU STAMP framework should also be able to authorise profit-oriented “champions” from the private sector.

Furthermore, the structuring of the Repurposing Platform (see Section 3.1.2) and the STAMP framework must be detailed. While the STAMP framework only provides for a protocol of cooperation between stakeholders to repurpose an off-patent API without needing new legal provisions, the Repurposing Platform is more ambitious as it seeks to integrate the scientific, methodological, financial, legal, regulatory and intellectual property aspects of the repurposing approach. Thus, the European Repurposing Platform should be a single public-private platform established as the main instrument for stimulating cooperation and coordination among public and private stakeholders for the testing and adoption of off-patent repurposing opportunities. Thus, pharmaceutical companies would be in position to take the lead. An organisation managing the Platform could be built, financed by its participants.

More specifically, as the Repurposing Platform aims to attract worldwide investment in the EU, it should include a funding programme for common projects, involving both private and public financial resources, with private investors predominating. It could be designed as follows:¹¹³ when a shareholder joins a project of the Repurposing Platform, it should comply with cost transparency. This condition would solve the ownership issue by correctly defining the balance of influence and power between all the shareholders of a repurposing project. Any stakeholder (pharmaceutical companies,

¹¹² Sijmen A. Reijneveld, [Public-private partnerships in public health research: does it work and if yes, how?](#), European Journal of Public Health, Volume 22, Issue 2, April 2012, Pages 165–166, abstract.

¹¹³ Funding programme inspired by the Fair Medicine organisation – a Dutch non-governmental organisation gathering stakeholders in the health sector such as hospitals, pharmaceutical companies or public administrations to improve access to safe, effective and affordable pharmaceuticals – which integrally fund repurposing projects. So far, no information has been disclosed on the projects themselves Fair Medicine, [Mission & Organisation](#).

patients, hospitals, research centres, etc.) could be a shareholder. The public sector could contribute to any projects, but only in a limited fashion for each project, thereby maintaining the private-sector approach to repurposing project management, that of maximising profits.

The Repurposing Platform should also implement regulatory pathways with features similar to the UK's ILAP, in line with the experimental nature of the STAMP framework. The Pharmaceutical Committee should therefore agree upon a more flexible protocol than the one voted in 2019 and introduce it to the Repurposing Platform. These tailor-made regulatory pathways would constitute a decisive factor for attracting innovative pharmaceutical companies because they have the potential to reduce time to market. Outside the Repurposing Platform, the Commission could in parallel encourage EMAs and national competent authorities to develop pilot regulatory projects, with features similar to the UK's ILAP, whereby repurposing opportunities could also opt to follow national regulatory pathways, depending on the population they are targeting for instance. Nevertheless, if the repurposed off-patent pharmaceutical is expected to be very innovative – which means its health technology assessment shows a strong added value – MAHs should opt to use the European centralised procedure,¹¹⁴ rather than national one. Fees and the duration of market authorisation processes should be clarified by the EMA as is the case for the current market authorisation applications.¹¹⁵

The ex-ante incentives in the EU STAMP framework, the future EU Repurposing Platform and the UK Repurposing Programme are necessary but not, however, sufficient to create a favourable environment for repurposing off-patent APIs. The pharmaceutical industry still lacks positive profitability expectations and faces the opportunity cost of making a better investment elsewhere, with a higher chance of profit. In both the UK and the EU systems, ex-post incentives are either absent¹¹⁶ or reduced to a few repurposing opportunities¹¹⁷ and this may explain why both are lagging behind the USA in terms of off-patent innovation.

Regarding market protection, a wider base of off-patent APIs, potentially benefitting from market protection, coupled with a sufficient period of regulatory data exclusivity in which to make profits, would be an adequate instrument to incentivise pharmaceutical companies to repurpose because it would broaden the market potential defined by prices and the targeted population. Orphan and paediatric incentives (see Section 3.1.1) are too specific, and the 1-year market protection granted in the EU for well-established substances (see Section 3.1.1) never resulted in new indications in the EU.¹¹⁸ The EU should therefore revise its set of market protection measures to include repurposed off-patent pharmaceuticals, notably by extending the “data ownership” provisions applicable to repurposing companies, for newly approved repurposed off-patent pharmaceuticals, from one to four years (Art. 10 (5) of the Directive (EC) 2001/83). This would give an advantage to the EU compared to the USA where market protection does not exceed 3 years for repurposed off-patent pharmaceuticals under Section 505(b)(2) (see Section 4.1). This could incentivise pharmaceutical companies, performing off-patent

¹¹⁴ EMA, [Authorisation of medicines](#).

¹¹⁵ For fees: EMA, [Fees payable to the European Medicines Agency](#). For market authorisation durations: EMA, [The evaluation of medicines, step-by-step](#).

¹¹⁶ The UK excludes favourable prices or reimbursements for repurposed off-patent pharmaceuticals. See Section 3.2.1 for more details.

¹¹⁷ The EU only grants relevant market protection to repurposed orphan pharmaceuticals. See Section 3.1.1 for more details.

¹¹⁸ No submission of any new indication for well-established substance as of June 2017. European Commission, [Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe](#), 2021, p. 62.

innovation elsewhere, to relocate their R&D activities to the EU as a European establishment is required in order to apply for marketing authorisation in the EU.¹¹⁹

It may potentially be appropriate to price and reimburse repurposed off-patent pharmaceuticals which tackle unmet needs in the health sector, without significantly affecting the cost-effectiveness of healthcare sustainability systems. Value-based premiums, like the one introduced in the Belgian legislation (see Section 4.2), are instruments of interest allowing pharmaceutical companies to handle repurposing opportunities where there is a large market potential. Therefore, the EU should engage in a discussion with Member States on pricing and the reimbursement of repurposed off-patent pharmaceuticals with added value, taking particular account of the Belgian value-added premiums for off-patent pharmaceuticals, with the aim of establishing EU guidelines. These guidelines could determine the burden-sharing between patients and the public sector to finance these premiums.

6 Conclusion

Off-patent innovation in the pharmaceutical sector represents a largely untapped source of innovation to tackle unmet needs. The EU is lagging behind the US in this domain. Off-patent innovation in the EU is lacking because of a lack of incentive to repurpose off-patent APIs in the EU. Therefore, the EU should use the UK Repurposing System as a basis for further development as this would support the industry during the marketing authorisation process, by providing public money and regulatory assistance. The EU STAMP framework should also be able to authorise profit-oriented “champions” from the private sector. A single public-private European Repurposing Platform should be established as the main instrument for stimulating cooperation and coordination among public and private stakeholders for the testing and adoption of off-patent repurposing opportunities. That platform should include a funding programme for common projects, involving both private and – due to the lack of profitability of off-patent pharmaceuticals – public financial resources, with a predominance of private investors. The EU should revise its set of market protection measures to include repurposed off-patent pharmaceuticals, notably by extending the “data ownership” provisions, applicable to repurposing companies for newly approved repurposed off-patent pharmaceuticals, from one to four years. The EU should engage in a discussion with Member States on the pricing and reimbursement of repurposed off-patent pharmaceuticals with added value, taking particular account of the Belgian value-added premiums for off-patent pharmaceuticals, with the aim of establishing EU guidelines.

¹¹⁹ EMA, [pre-authorisation guidance: 1.2 How can i tell if I am duly established in the EEA as an applicant?](#), 10.2020.

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