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Innovation in Known Drugs—The European Angle

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INNOVATION IN KNOWN DRUGS –
THE EUROPEAN ANGLE

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ABSTRACT

Research into new uses for known drugs should be encouraged because the “repurposing” of known drug molecules can be a highly effective route of innovation for pharmaceutical companies. Investment in the development of these products should be rewarded. However, incentives that are designed to reward innovation must be in line with the size and value of the innovation in order to maintain a sustainable balance between incentivizing research and developing and encouraging a competitive market. In the context of encouraging innovation of new uses for known drugs, factors that facilitate access to drug development and innovation should also be considered in addition to incentives.

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INTRODUCTION

Both innovative and generic pharmaceutical companies may invest in research into new uses for known drugs. This “repurposing” of known drug molecules can be an effective route for innovation. Most importantly, it takes advantage of the extensive body of knowledge, research, and clinical experience that has already been gained through the use of known treatments. By combining this body of data with technological advances made since the discovery of a given drug molecule, significant and previously unknown uses for such drugs may be uncovered.

The future of the pharmaceutical industry, and the patients who rely on it, depends on the continuous development of new and improved treatments. Innovation is important—this is as true for the generic medicine sector as it is for “innovative” pharmaceutical companies. Generic pharmaceutical companies depend on innovation in the pharmaceutical industry, and recognize that innovation can be risky and may require substantial investment in research and development. Such investment should certainly be rewarded. However, it is important to maintain a fair balance between rewarding innovation and assuring patients’ access to affordable healthcare. Incentives designed to reward innovation must be in line with the size and value of the innovation in order to maintain a sustainable balance between the goal of incentivizing innovation and of rationalizing health care budgets through generic entry into the market.

Despite the above, generic pharmaceutical companies are often characterized as opposing incentives for innovation. This may be because their business models sometimes comprise of bringing legal challenges with the aim of invalidating exclusivities that are designed to provide incentives to innovate. However, it does not follow from this that generic companies do not support incentives for innovation. In fact, the reverse is true: generic companies support sensible rewards and incentives for innovation. What they oppose are rewards disproportionate to the actual degree of innovation and amount of effort required to benefit from the reward, and the abuse of such incentives to prevent the legitimate market entry of competitors.

Systems currently exist to govern how medicines are developed, licensed, protected, and priced; each has the potential to encourage or,

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if mismanaged, to stifle innovation. In Europe, the development of novel medicinal compounds is incentivized and rewarded in a way that is regarded by industry and effective and beneficial overall. However, incentives and rewards are not as beneficial or effective when they concern innovations in treatment made from developing already-known substances for new uses, formulations, methods of delivery and so on.

This Article focuses on the development of new treatments by the repurposing of known drugs. The debate on how to encourage innovation in this area usually centers on the incentives available for repurposed drugs. This Article considers such incentives, but also looks at another important aspect: how access to various key components of the field—such as data, funding, and skills—can be critical to the successful development of a repurposed drug product. It suggests that the current system of incentives is unbalanced, with new active substances receiving extensive protection and with innovations based on development of known active substances receiving little or effectively no reward.

It is possible to strike a better balance between encouraging innovation in known drugs by rewarding innovation and improving access to data and other key elements, and allowing for optimal access to the market to the benefit of all stakeholders. Industry and payors—primarily the National Health Services of the Member States in Europe—have the same goals: providing broad availability of fairly priced quality medicines. Patients often want new treatments, but would also benefit from treatments that could be developed from known medicines, which could be made available more quickly due to their confirmed safety. These may also offer other advantages over the older drug, such as being more convenient to take or having a more convenient dosing regimen.

More can be done better to incentivize patient-focused development of known drugs. A new system of incentives should recognize that developing known drugs may be cheaper and require less investment while nevertheless providing a marked improvement in patient care. This Article proposes that a reward system where the duration and extent of the reward is tied to the size of the innovation would ultimately benefit the industry.

The pharmaceutical industry is capable of repurposing drugs. In particular, generic companies are well-positioned to make patient-focused developments of known treatments. Generic companies are

particularly focused on understanding the demands of the market and delivering products that the market wants in a competitive, non-exclusive and at times, commodity-driven environment. Payors also benefit from such innovations; patients who understand their treatment regimens and better comply with them may save Health Services money by putting fewer demands on healthcare providers.¹ However, without effective reward for the investment in identifying and developing these sorts of innovation, companies may not pursue opportunities, for fear that they may fail to deliver sufficient financial return.

I. INCENTIVES – ISSUES AND POTENTIAL SOLUTIONS

The pharmaceutical industry plays a unique role in the functioning and advancement of society; that role is recognized in the particular systems of reward, authorization, and pricing for health care products. In particular, the high cost of development of new treatments versus the relatively low cost to third parties of copying such discoveries means that a robust scheme of protection of innovation is needed in order to reward investment in new treatments for patients. Such a scheme has been developed through the patent and regulatory systems which reward innovation through the granting of exclusivities which provide a market monopoly for a fixed period. However, for innovations in treatment that arise from repurposing known drugs, these same systems are not always as effective. This is not a result of a deliberate policy to offer less protection to repurposed drugs,² but because current systems offer inadequate protection and certainty. If investment in new uses for known drugs is to be encouraged, this situation must change. Although the development of a repurposed drug would usually be more straightforward than the development of an entirely new drug, it may still require substantial effort and investment. It is therefore important to provide incentives for

¹ Aurel O. Iuga & Maura J. McGuire, *Adherence and Health Care Costs*, 7 RISK MGMT. & HEALTHCARE POL'Y 35 (2014), <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3934668/>.

² The “new” use of a repurposed drug may sometimes be referred to as a “second medical use”.

258 WASHINGTON JOURNAL OF LAW, TECHNOLOGY & ARTS [VOL 12:3 investment, though any such incentives should of course be proportionate to the effort and investment required to develop the repurposed product.

In Europe, the market protection available for medicinal products may broadly be divided into two categories. The first comprises the intellectual property exclusivities awarded by the patent system. The second consists of the regulatory exclusivities available by virtue of the functioning of the regulatory legal framework i.e. the system for granting marketing authorizations for medicinal products as overseen by various Regulatory Agencies.

A. Issue: Patents³

1. The Current Framework

A patent provides the right to prevent others from selling, developing, manufacturing or distributing a product, or from conducting a process, that is covered by the patent in question.⁴ The term of European patent protection is twenty years from the filing date.⁵

The product or process described in the patent must be both novel—that is, not described anywhere in the world prior to the priority date of the patent—and inventive—that is, “not obvious” to a hypothetical non-inventive skilled person.⁶ The invention must also

³ This section discusses a number of different cases relevant to the patent protection that is available for repurposed medicines. This article does not provide an exhaustive review of the case law in this area and the cases mentioned are only discussed in order to provide illustrative examples of the problems that have been encountered in this field.

⁴ Acts that infringe a European patent are governed by national law *see* Convention on the Grant of European Patents (European Patent Convention), art. 63, Oct. 5, 1973, 1065 U.N.T.S. 255, as amended by the Act Revising the European Patent Convention, Nov. 29, 2000, available at [http://documents.epo.org/projects/babylon/eponet.nsf/0/00E0CD7FD461C0D5C1257C060050C376/\\$File/EPC_15th_edition_2013.pdf](http://documents.epo.org/projects/babylon/eponet.nsf/0/00E0CD7FD461C0D5C1257C060050C376/$File/EPC_15th_edition_2013.pdf). The relevant national law in the United Kingdom, for example, is the Patents Act, 1977, ch. 37, § 60.

⁵ *Id.* at art. 63.

⁶ *Id.* at art. 54 and 56.

be clearly disclosed:⁷ enabling the public to perform the invention once the term of protection has expired is the *quid pro quo* for providing the monopoly. Finally, the inventions must be “patentable subject matter”, that is subject matter that is not excluded from protection.⁸ The patent system therefore protects adequately disclosed innovation in the literal sense of inventions that are “new” and “not-obvious”. Drugs that consist of novel chemical compounds are invariably protected by patents and therefore the developer of the drug benefits from a twenty-year monopoly, during which no competitor can produce a generic version of the drug.⁹

In the pharmaceutical sector, extensive research and testing is necessary for the development of medicines. Further, regulatory approval is required before a medicine can be placed on the market.¹⁰ Due to the increasing complexity of medical research and development, and to compensate for the extensive period of time needed to obtain a regulatory approval, the European Parliament introduced a Supplementary Protection Certificate (“SPC”) system,¹¹ which enabled the granting of additional protection to medicinal products in the form of a product-specific extension to the term of the patent.¹² This enables the approved product that resulted from the development and regulatory approval process to benefit from the protection of the patent for an additional period of up to five years.¹³ This system provides compensation for the delay caused by the regulatory approval process in reaching the market by enabling a

⁷ *Id.* at art. 83.

⁸ *Id.* at art 53. (listing certain things which may not be patented).

⁹ See *supra* note 6.

¹⁰ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, art. 6, 2001 O.J. (L 311) 67.

¹¹ The current European legislation that governs SPCs is Regulation EC No. 469/2009, which replaced Regulation EC No. 1768/92.

¹² Regulation (EC) No. 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products, art. 4, 5 and 13, 2009 OJ (L 152) 1.

¹³ *Id.* at art. 13.

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longer presence on the market without generic competition.¹⁴ Since
SPCs are patent-based rewards, and provide an extension in duration
of the patent term based on the timetable to grant of marketing
authorization for a medicinal product protected by that patent, it is in
some senses a “hybrid” reward: based on both the patent protection
over a product and the marketing authorization granted to that product.

2. Patent Protection for Repurposed Drugs

It has long been recognized that the patent system appears to be
inadequate to protect discoveries based on the development of known
drugs.¹⁵ The first attempt in Europe to implement a system whereby it
was possible to patent the invention of second medical uses for known
products was the introduction of Swiss type claims. These were
introduced under the European Patent Convention of 1973 and were
so named because they were based on the advice and practice of the
Swiss Patent Office.¹⁶ They allowed the granting of patents for second
medical uses of known substances provided the claim was drafted in
the following format:

“Use of substance [X] for the manufacture of a
pharmaceutical composition for new therapeutic
application [Y].”

Their purpose was to turn subject matter previously excluded from
patentability—specifically, methods of treatment of the body—into
patentable subject matter. This is achieved by granting a claim that is
a joint product-and-process claim—albeit one that incorporates the
use for which the product and process is conducted. Swiss type claims
were superseded by the introduction of the European Patent
Convention 2000.¹⁷ Second medical use claims under the EPC 2000

¹⁴ *Id.*

¹⁵ See Mr. Justice Jacob, *Teva Pharmaceutical Industries Ltd v Istituto Gantili Spa & Ors* [2003] EWHC 5 (Pat), and the overview of the problem provided by Scott Parker and Ben Hall, *Skinny labelling infringement: finding a fair remedy*, INTELLECTUAL PROPERTY MAGAZINE (Sept. 3, 2013), <http://www.intellectualpropertymagazine.com/patent/skinny-labelling-infringement-finding-a-fair-remedy-91356.htm>.

¹⁶ Approval was given in decision G5/83 dated 5 December 1984.

¹⁷ Convention on the Grant of European Patents (European Patent Convention),

are typically in the format:

“Use of substance [X] in new therapeutic application [Y].”¹⁸

For some time, it was also uncertain whether SPCs could be available for repurposed medicinal products. However, the decision of the Court of Justice of the European Union in the *Neurim* case confirmed that such protection is available.¹⁹ The case concerned the medicinal product melatonin, which had first been authorized as a treatment for the control of seasonal breeding in sheep.²⁰ *Neurim* had subsequently obtained patent protection and a marketing authorization for melatonin for treatment of insomnia in human adults.²¹ The question for the Court was whether the first authorization to place the product on the market in the EU for the purposes of granting an SPC was the authorization for the veterinary product. If that had been the case, then an SPC would not have been available. The court found that, in practice, the first authorization for use in animals had offered no assistance to *Neurim*, for whom it had taken fifteen years to get their melatonin product to the market. The effect of the Court of Justice decision was that *Neurim* could be rewarded, through the granting of an SPC, for their work on developing melatonin for use in humans despite the fact that melatonin was a known drug that had previously been used in animals.

As discussed above, European legislators have decided that discoveries of second medical uses for medicinal products should be protectable under the patent system.²² Authorities that grant patents have introduced the necessary architecture to grant such patents. However, this has led to cases where courts attempt to reach the “right” decision, but in doing so complicate this area of law. The *Neurim* SPC case is one such example. This creative interpretation of

art. 54(5), Oct. 5, 1973, 1065 U.N.T.S. 255.

¹⁸ European Patent Office Guidelines for Examination, Part G, Chapter VII, Section 7.1.

¹⁹ *See, e.g.*, Case C-130/11, *Neurim Pharmaceuticals (1991) Ltd v Comptroller-General of Patents*, 2012 E.C.R.

²⁰ *Id.*

²¹ *Id.*

²² *See supra* notes 17, 18 and 19.

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the SPC Regulation was at odds with the black letter of the law as well as numerous earlier SPC cases. This has led to some uncertainty in other SPC cases and the necessity for further references by national Courts to the Court of Justice of the European Union.

3. Problems with Patent Protection for Repurposed Drugs

Despite the checkered history of patent protection for repurposed drugs, it is now accepted that patents which protect second medical use claims are acceptable and that SPCs for such claims may be available. Further, courts have recognized that it is possible to obtain a patent and an SPC to protect a repurposed drug.²³ However, the utility of these exclusivity rights may still be compromised due to problems relating to validity and enforceability. Both of these issues have been considered by national Courts in Europe.

In the English case of *Merck v. Teva & Arrow*,²⁴ Mr. Justice Jacob commented on the validity problem. The drug at issue was alendronate, which was discovered and used in the 1960s but was repurposed in the 1990s for treatment of osteoporosis.²⁵ Two secondary medical use patents were challenged in the case. Both were found to be invalid because of work done with a precursor compound of alendronate called pyrophosphonate.²⁶ Jacob found that this work meant the patents must be invalid because it rendered use of alendronate for the treatment of bone loss obvious.²⁷ In his judgment, commenting on his finding that both patents were invalid, Jacob said:

“I do so with some regret. Merck have only had a few years' exclusive exploitation of alendronate. They must surely have had to make a very considerable investment and incurred considerable risk in bringing it to market. And mankind is better off as a result.”

“But the patent system does not confer monopolies on

²³ See supra note 20.

²⁴ [2003] EWHC 5 (Pat).

²⁵ *Id.*

²⁶ *Id.*

²⁷ *Id.* at paragraphs 36 to 64. Note that the patents were also found invalid for lack of novelty and because it was a method of treatment of the human body by therapy.

those who develop obvious or old products, even if they have never been exploited. A workable system for that might be a good idea, particularly in the field of medicine and analogous fields.”

The problem with enforcement of second medical use patents is illustrated by a decision of the Dutch Court of Appeal at The Hague in preliminary relief proceedings regarding Novartis’ zoledronic acid product.²⁸ The patent concerned a second medical use of zoledronic acid for the treatment of osteoporosis and the delivery mechanism and dosage form of such. The first known—and no longer patented—use for the drug was treatment of Paget’s disease. The Novartis marketing authorization for Aclasta contained indications for treatment of osteoporosis and Paget’s disease.²⁹ Sun Pharmaceuticals, had obtained a marketing authorization for its generic zoledronic acid product with a so-called “skinny label” for the treatment of Paget’s disease only. A “skinny label” is a term used for a generic marketing authorization where one or more patent-protected indications granted to the reference product have been excluded deliberately from the generic label. Skinny labeling is provided for in Directive EC 2001/83—often referred to as the “Medicines Directive”—to account for just such a situation.³⁰ The idea is that a product with a skinny label will not infringe patent rights because it does not instruct the user to use the product in a way that would infringe the patent.

In this situation, it is clear, assuming the second medical use patent is valid, that the patent should be enforceable against use in the patented indication. However, it should not prevent market entry of a generic product for use in treating indications for which there is no patent protection in place. Taking the zoledronic acid example above, assuming the patent for use of zoledronic acid for the treatment of osteoporosis is valid, it ought to be possible to enforce it

²⁸ Court of Appeal The Hague in *Novartis AG v. Sun Pharmaceutical Industries*, 27 January 2015, case number C/09/460540 / KG ZA 14-185, ECLI:NL:GHDHA:2015:1769.

²⁹ *Id.* at paragraph 2.7

³⁰ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, art. 11, 2001 O.J. (L 311) 67.

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to prevent generic zolendronic acid products being used for the treatment of osteoporosis. In relation to other indications for which there is no patent protection, such as Paget's disease in the zolendronic acid example, generic products should not be prevented from being used. Skinny labeling of generic products deals with this problem in theory as a skinny label excludes any patented indications. Therefore generic products with a skinny label are not authorized for use in the patented indications. However, although a skinny label can state that the product should be used for the non-patented indications only, in practice this does not necessarily prevent prescribing, dispensing, and use of the generic product in patented indications. The producer of the generic product does not have any control over how its product is prescribed, dispensed, and used once it is on the market. It seems unfair to penalize them via patent enforcement litigation if the generic product ends up being used for patented indications. On the other hand, a patentee ought to be able to enforce its patent.

In the Novartis case, the Dutch Court of Appeal decided to approach this issue by considering whether, despite the use of the skinny label, Sun knew or should have known that its product would be used in a way that would infringe the patent—i.e. that it would be used to treat the patented indications.³¹ The Court of Appeal found that, notwithstanding the skinny label, Sun knew or should have known that its product would be used for the patented indications: the amount of product it supplied far exceeded the amount that would be needed to meet patient need for the Paget disease indication. As a consequence, the Court of Appeal held that Sun had conducted contributory infringement of Novartis' patent, and handed down a preliminary injunction against Sun. (In a more recent decision in parallel proceedings on the merits, the Hague District Court has in an interim decision held, on different grounds, that Sun had not conducted contributory infringement of Novartis' patent³², but that it

³¹ Court of Appeal The Hague in *Novartis AG v. Sun Pharmaceutical Industries*, 27 January 2015, case number C/09/460540 / KG ZA 14-185, ECLI:NL:GHDHA:2015:1769, paragraphs 4.33 - 4.34.

³² District Court The Hague in *Novartis AG v. Sun Pharmaceutical Industries*, 25 November 2015, case number C/09/469148 / HA ZA 14-770, ECLI:NL:RBDHA:2015:14337. The District Court held that because a Swiss type claim is a purpose limited process claim and its protection does not also cover the product itself, there can only be contributory infringement if a party

cannot be excluded that it has *directly* infringed the patent.³³)

The major problem with this approach, however, is a lack of certainty. A patentee should be able to assume that its patents will not be infringed, and third parties should be able to market a product for uses that are not patent-protected without either party having to rely on the Court to adjudicate.

Recent litigation in the UK High Court and Court of Appeal³⁴ concerning the drug pregabalin further illustrates this problem. In these proceedings, a number of the defendants had obtained market authorization for their generic products using skinny labels.³⁵ In this case, further measures were taken to prevent so-called off-label use, in addition to ensuring that the marketing authorization granted was for the skinny label only. One such measure was to write to the superintendent pharmacists of all UK Clinical Commissioning Groups, instructing them to inform their members that only Pfizer's brand product, Lyrica, was to be prescribed and/or dispensed for treatment of the patented indications.³⁶ The Court further sanctioned written guidance to NHS England—as representative of the National Health Service—which informed all prescribers and dispensers that they should only prescribe or dispense Pfizer's Lyrica for patented indications.³⁷ This litigation is still ongoing and so the issues are by no means finally settled.

Exclusivities for known drugs that have been repurposed are available, in theory, in the form of patent and SPC protection.

would supply an essential element knowing (or with reasonable grounds to know) that this element would be used by a third party in applying the protected process, i.e. manufacturing the drug. As Sun had only supplied the already manufactured drug, Sun could not be said to have supplied an essential element which would subsequently be used by third parties to manufacture the drug.

³³ *Id.* As the subject of direct infringement came up at a rather late stage of proceedings, the District Court refused deferred a decision on this aspect of the case, and requested parties to file additional deeds instead.

³⁴ Warner-Lambert Company, LLC v. Actavis Group PTC EHF & Others, [2015] EWHC 72 (Pat).

³⁵ *Id.*

³⁶ *Id.* from paragraph 78 onwards.

³⁷ *Id.*

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However, in practice, the enforcement of these exclusivities is highly problematic. This inherent uncertainty means that these protections do not provide an appropriate or suitable system for incentivizing the development of repurposed medicines.

B. Potential Solution: eHealth

Problems concerning the validity of second medical use patents are difficult to resolve through the patent system. These are perhaps better addressed by rewarding such innovations with regulatory exclusivity, as discussed below. Similarly, the problems with enforcement discussed above would be hard to solve through changes to the patent system itself. However, enforcement issues can be resolved by the increased use of eHealth³⁸ technologies solutions and technological support systems.

Take, for example, the problems that arise when attempting to enforce a second medical use patent where there are both patented and non-patented indications, and a generic company wishes to launch a product with a skinny label directed at the non-patented indications. This problem is illustrated by the zolendronic acid and pregabalin cases discussed above.³⁹ Such problems could be rectified by creating a new mandatory prescribing and dispensing system. Requiring prescriptions to include the indication for which the drug is prescribed would remove the uncertainty around whether generic products are being dispensed against patented indications despite using a skinny label. Those who dispense prescriptions would become the gateway towards ensuring that drugs are dispensed only as permitted. Such a system would act to tie the prescription and dispensing of a drug to its intended use. However, this scenario can only occur via mandating the prescriber's recording of the indicated use.

This system would help not only in ensuring that drugs are prescribed in line with patent needs, but would also make any damages claim easier to assess in the event of dispute about the validity of the patent. Prescribing and dispensing data would show not only how much of the relevant products were used, but would also show the

³⁸ eHealth is a term used to describe health care practices that are supported by electronic processes and communication.

³⁹ See supra notes 29 and 32.

proportion of the market that relates to each indication.

With the increased availability and sophistication of technologies (such as ePrescribing⁴⁰ and eHealth records) the infrastructure is in place for this data to be generated and accessed.

1. An Example: The Substitution System in Denmark

Some countries in Europe are already taking steps that create closer ties between patent protection and prescription decisions. In 2015, the Danish Health Authority implemented new rules on substitution for prescriptions.⁴¹ In Denmark, generic medicines are in the same “substitution group” as medicines that contain the same active substance in the same quantity and that are “used in the same way.”⁴²

Under this new regime, which came into place on the basis of the ruling of the Danish Maritime and Commercial High Court in the Danish pregabalin case, pharmacies are not to substitute a generic medicinal product for the brand if the prescription has been issued for the treatment of a patent-protected indication. the Danish Medicines Agency⁴³ is to notify pharmacies when a medicinal product has a patented indication. It is for the pharmaceutical companies to notify the Danish Medicines Agency in writing of such patent protection for its products.

On the other hand, pharmacies must substitute a generic medicine for the brand if the medicinal product has been prescribed for the treatment of a non-patented indication. This is only possible in a system where prescribers are required to note for what purpose the

⁴⁰ ePrescribing is a term used to describe computer based, generation of prescriptions and electronic transmission directly to the pharmacist.

⁴¹ The Danish Ministerial Order on Prescriptions, § 38 and § 38 a (the latter introducing the new regime).

⁴² The example given of medicines that are “used in the same way” is that tablets and capsules are both for oral intake.

⁴³ The Danish Health Authority was recently split up into four different authorities and the relevant authority today is the Danish Medicines Agency. The Agency has in this connection invited the pharmaceutical companies to make the Agency aware of they are the proprietor of a patent on a specific indication, but this is not included as such in the law.

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drug is being prescribed.

2. Confidentiality Concerns

The desire to protect patient confidentiality may be seen as a reason to oppose prescription by indication. If such a system is to work, robust data protection regimes will be necessary. Technological advances should reassure patients that their personal health information is secure and will remain confidential. After dispensing, there is no need to maintain a link between the individual and the prescribed product simply for purposes of recording and analyzing data on the number of prescriptions dispensed for each indication. The data should be anonymized before it enters a database that for monitoring prescriptions by indication that could potentially be used to facilitate the enforcement of patents for repurposed drugs.

C. Issue: Regulatory Exclusivity

1. The Current System

The medicines regulatory system is harmonized in Europe. The European Medicines Directive⁴⁴ rewards the investment and risk of bringing a product to market with a prescribed period of time, during which no unauthorized third party may obtain a generic marketing authorization for the same medicinal product.⁴⁵ The reward of regulatory protection may therefore incentivize investment without the onerous patent system requirements of novelty and inventive step. Regulatory exclusivities can be a powerful tool for marketing authorization holders that can be enforced against third parties. In 2014, the Court of Justice in the European Union in the Olainfarm case⁴⁶ gave judicial backing to the right of marketing authorization holders to challenge the grant of marketing authorization to third parties in breach of regulatory exclusivity.

A market authorization holder benefits from the period of

⁴⁴ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, 2001 O.J. (L 311) 67.

⁴⁵ *Id.* at art. 10.

⁴⁶ See C-104/12, Olainfarm (Judgment), 2014 ECR.

marketing and data exclusivity that attaches to a new product authorized under a “full” application. A full application must include substantial safety and efficacy data generated from large scale clinical trials. This route to gaining marketing authorization is usually only used for the approval of new drugs where there is no pre-existing safety and efficacy data, and so significant data must be generated by the company developing the drug.

Any new products authorized via a full marketing authorization application made since November 20, 2005 benefit from a period of eight years of “data exclusivity”, during which no third party may rely on the data provided in the marketing authorization dossier for the purposes of obtaining a generic marketing authorization.⁴⁷ The period runs from the date of marketing authorization grant. There is a concurrent ten-year period of “market exclusivity” during which the third party cannot use its authorization to market the generic product for another two years. This period holds even if the third party has obtained a generic marketing authorization by relying on the data in the reference product dossier following the expiry of the eight-year data exclusivity term.⁴⁸

The regulatory protection system contains further mechanisms that aim to incentivize research and development of novel products, and to some extent try to incentivize further development of products that have already received marketing authorization. These are described briefly below.

a. +1 Market Exclusivity

If a marketing authorization holder produces the necessary data to show safety and efficacy for an authorized product in a new treatment indication within the first eight years of authorization, they will be rewarded with an extra year of market exclusivity.⁴⁹ This means that, where a holder could produce the safety and efficacy data, the

⁴⁷ See supra note 41.

⁴⁸ *Id.*

⁴⁹ Council Directive 01/83, art. 10(1), 2001 O.J. (L 311/67) (EC).

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medicinal product would benefit from eleven years of market
exclusivity in total.⁵⁰

One year of data exclusivity is also available for prescription
products that are reclassified to products available over the counter as
a result of significant pre-clinical tests or clinical trials.⁵¹

In addition, one year of data exclusivity is currently available for
new indications developed for well-established substances provided
that “significant” pre-clinical or clinical studies have been carried out
in relation to the new indication.⁵²

b. Orphan Market Exclusivity

In 2001, new European legislation introduced a reward of market
exclusivity for companies that developed drugs for treatment of so-
called “orphan conditions.”⁵³ This legislation was designed to
incentivize discovery of treatments for conditions that would not
otherwise garner the interest of pharmaceutical companies, either
because there are a very small number of patients who would require
such treatment or because of other factors that mean the treatment area
would otherwise not receive financial investment.⁵⁴

Orphan market exclusivity lasts for ten years from the grant of
market authorization of the product for the orphan indication.⁵⁵ It
differs from the scope of data and market protection offered to non-
orphan products. It is in one sense narrower in that it protects only the
orphan indication. It does not, for example, prevent a third party from
obtaining a marketing authorization for the same product in a different
indication. It is, however, broader in scope and duration than “normal”
data exclusivity and market exclusivity because it prevents regulatory
authorities from accepting an application for a marketing
authorization for any similar medicinal product in the same indication
for a period of ten years.⁵⁶ Exclusivity is therefore granted, not just for

⁵⁰ *Id.*

⁵¹ *Id.* at art. 74(a)

⁵² *Id.* at art. 10(5)

⁵³ Council Regulation 141/2000, 1999 O.J. (L 18/1) (EC) (the Orphan Regulation).

⁵⁴ *Id.* recitals.

⁵⁵ *Id.* at Article 8(1).

⁵⁶ *Id.*

identical products—but also for similar products.

c. PIPs and Pediatric Extensions

All medicines for which marketing authorization applications were made on or after July 26, 2008, are required either to have research conducted into the safety and efficacy of the drug in pediatric populations by completing an agreed pediatric investigation plan (“PIP”), or to agree to a waiver.⁵⁷ The waiver exception may apply where it would be unnecessary or inappropriate to conduct studies in pediatric populations or where it may be shown that the treatment does not represent a significant therapeutic benefit over existing treatments for pediatric patients.

Completion of the PIP brings with it reward, even if it fails to lead to the authorization of a pediatric indication.⁵⁸ The type of reward obtained for PIP completion depends on the regulatory status of the product in question. For non-orphan designated products that are protected by an SPC (or a patent that is eligible for grant of an SPC) the patent holder will be rewarded with a six-month extension of their SPC.⁵⁹ For orphan designated products, the term of orphan market exclusivity will be extended from ten to twelve years.⁶⁰

The pediatric medicines legislation also introduced pediatric use marketing authorizations or PUMAs.⁶¹ These are a dedicated marketing authorization for medicinal products indicated exclusively

⁵⁷ Council Regulation 1901/06, 2006 O.J. (L 378/1) (EU). This regulation is referred to as the “Pediatric Regulation.” There were also provisions introduced in this Regulation to require that MA holders who wished to add new indications, including pediatric indications, new pharmaceutical forms and new routes of administration to their MA would be required to complete a PIP, even for products for which the MA application was made prior to 26 July 2008.

⁵⁸ Provided that the results of the studies conducted are reflected in the summary of product characteristics and, if appropriate, in the package leaflet of the medicinal product. See *Id.* at art. 36, 37.

⁵⁹ Council Regulation 1901/06, art. 36, 2006 O.J. (L 378/1) (EU).

⁶⁰ *Id.* art. 37.

⁶¹ *Id.* art. 30.

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for use in the pediatric population, or subsets thereof. PUMA applications benefit from an 8 + 2 period of data and market protection. They are also eligible for a partial exemption from certain application fees.⁶² In fact, PUMAs serve as an example of a regulatory exclusivity right incentive system that has been largely ineffective. Industry was not convinced that a PUMA would prevent off-label use of the earlier product authorized within the PUMA product's pediatric indication. As such, very few companies have shown an interest in PUMA authorization.

2. Regulatory Exclusivities for Repurposed Drugs

Some of the regulatory measures to incentivize development of already authorized medicines appear successful. For example, a great number of marketing authorization holders have conducted the work necessary to obtain the +1 market exclusivity extension for adding a new indication of "significant clinical benefit" within the first eight years of grant of the marketing authorization. The year of exclusivity available for new indications for well-established substances may provide some incentive for developing new indications for known drugs. However, the number of indications actually approved via this route seems to be relatively few, suggesting that it is not a particularly effective incentive. The year of exclusivity available for prescription products that can be converted to over-the-counter products bestows a real advantage in that market. The pediatric legislation has also generated treatments for pediatric populations that would not otherwise have been investigated and authorized. The legislation makes such work a requirement for the grant of a marketing authorization, (subject to any waiver) but the incentives on offer are attractive to marketing authorization holders.

Unfortunately, the regulatory system in Europe does not yet contain effective incentives for the development of known drugs once the initial 10 + 1 year period of regulatory exclusivity has expired. The legislation stipulates that all developments of a given medicinal

⁶² European Medicine Agency Questions and answers on the paediatric use marketing authorisation (PUMA) EMA/753370/2011 Rev 1, at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/09/WC500112071.pdf

product made by the original developer (e.g. new indications, new methods of administration, dosing regimes, etc.) will fall within what is known as the same “global marketing authorization” (“GMA”) for that product.⁶³ The date of the first authorization is the date from which the regulatory exclusivity attaching to all of the products within the same GMA will run. The purpose of the GMA concept is to prevent marketing authorization holders from effectively extending the monopoly enjoyed by their product by obtaining new periods of regulatory exclusivity for every minor development of their product. This is sometimes referred to as “evergreening”. Assuming there is no patent protection in place, this allows generic products to compete effectively with the original product once the relevant period of regulatory exclusivity has expired. But, on the other hand, it leaves little room for reward for a genuine innovation related to a repurposed drug. Currently, the protection provided by regulatory exclusivities is inadequate incentive in itself to promote investigation into new uses for known drugs.

D. Potential Solution: A New Market Exclusivity Right

It would be perfectly possible to devise a new market or data exclusivity right to protect repurposed drugs. The reward available should be proportionate with the size and/or value of the innovation. For example, the duration of the exclusivity can be shorter for innovation in known compounds than it is for new compounds. To achieve this, it may be necessary, as with the orphan medicinal product system, to show that certain requirements are met in order to receive the reward of exclusivity. For example, the treatment provides

⁶³ Council Directive 01/83, art. 6(1), 2001 O.J. (L 311/67) (EC) (The only way that a follow on product e.g. isomer, mixture of isomers, complex or derivative or salt of a previously authorized subject can come outside of the GMA of the earlier product is if the applicant can show that the development differs in properties with regard to safety and efficacy from the substance previously authorized).

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a significant benefit over pre-existing treatments and/or the treatment meets an otherwise unmet need. This reward is much more flexible as compared to the patent system.

Without changes to prescribing and dispensing systems, the enforcement of any such new regulatory exclusivity right would run into the same sorts of problems as are currently seen in the enforcement of second medical use patents. The earlier authorized product will still be open to generic competition at some stage during the regulatory exclusivity of the later developed product. It may be that the earlier product is open to generic competition prior to authorization of the later product. Assuming that the dosage forms and strengths, etc. are equivalent, the difficulty, as with the patent system, is in preventing off-label use of the earlier authorized product for the newly discovered use. This makes the market for the “repurposed product” substantially less attractive than for a new medicinal product. A new market exclusivity right would only provide an attractive reward and therefore an effective incentive for repurposing of known drugs if it were coupled with a system of mandatory prescription by indication, as discussed above in relation to the enforcement of patent protection. Such a system would ensure that only the developer of the repurposed product would benefit from the new prescriptions and increased market generated by the development of the repurposed drug.

E. Issue: Pricing and Reimbursement

The price that can be achieved for any pharmaceutical product is a key incentive for developing it and bringing it to market. In Europe, procedures for determining the pricing and reimbursement of medicines are not harmonized. Pricing and reimbursement are therefore set through the different health schemes in each country and the applicable rules differ in each country. Nevertheless, some broad observations about pricing and reimbursement in Europe can be drawn. Most national price and reimbursement systems and legislation in Europe focus on cost containment measures and do not currently incentivize the development of repurposed drugs.

As things currently stand, it is very difficult to get a premium price for a repurposed drug product. If the drug is known, and there is no patent protection covering the repurposed drug, the product will most likely get a generic price. It is doubtful that the payers will even

engage in a discussion about the added value that such repurposed drugs can provide. These drugs are likely to be clustered with the pharmaceutical products containing the same active substance no matter how beneficial they are to the patients and society as a whole. It may be also possible—for example in Germany—that such drugs will be tendered together with price being often the only differentiating selection criteria and taking no notice of the additional patient health benefit.⁶⁴

Even if the repurposed drug is covered by a patent, it is questionable whether the developer will be able to get a premium price for repurposing these medicines. Below, two different types of repurposed drugs provide examples of how the current system may preclude them from gaining a price that reflects the investment that must be made to develop them.

1. New formulations

New formulations can provide significant benefits to patients. For example, reformulating a drug that needs to be injected into one that can be taken orally as a tablet provides increased convenience for the patient and is likely to improve patient compliance with the course of treatment. Despite these potential benefits for patients, the price of reformulated drugs is usually based on a benchmark of the price of the old product.

Germany is a good example of a country where the benchmark for the price of a new formulation is the price of the old product. Indeed, in 2003 a mandatory manufacturer's rebate of 6 percent was introduced in Germany (which has been increased up to 16 percent from 2010 to 2014, currently reduced to 7 percent). It applied to patented medicinal products, available on prescription only, for which no reference price group exists and which are dispensed by community pharmacies or hospital pharmacies for the out-patient sector. In context of this regime, the German legislator also introduced a price moratorium in 2010, which rules that newly introduced medicinal products identical in active substance and

⁶⁴ See *E.g.*, decision of the 2nd Public Procurement Tribunal on 29 January 2015 (VK 2 – 119/14); see also Section 130a (8) Social Code Book 5.

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comparable in pharmaceutical form to medicinal products already placed on the market in the past by the same pharmaceutical entrepreneur, may only be priced on the basis of the initial product; a new indication is not relevant.⁶⁵ A significant increase from 6 to 16 percent was imposed in 2010 and in order to avoid circumventions of this rebate by increasing the price, a “price moratorium” was created at the same time.⁶⁶ According to this price moratorium, newly introduced medicinal products identical in active substance and comparable in pharmaceutical form to medicinal products already placed on the market in the past by the same pharmaceutical entrepreneur, may only be priced on the basis of the initial product. The price moratorium and the respective anti-avoidance regulation therefore apply to new formulations, which must be priced on basis of the price of the first product. This cost containment regime applies regardless of whether the new formulation is also authorized for additional indications.

Under this German rebate regime, the price may actually be lower for the new or improved formulation. Supposing that a company developed a new dosage regimen of a known drug that involves less active substance than the original product, the company would be likely to obtain a lower price for the new formulation. Indeed, the price of the new formulation will be proportionate to the amount of active substance in the pharmaceutical product.⁶⁷ Therefore even though the new formulation is more convenient for the patient and less likely to trigger adverse events, it will get a price lower than the price of the original product.

Another example comes from Poland, where the local medicines regulations require that the first “equivalent” of an authorized medicine must be priced 25 percent lower than the earlier authorized drug in the first authorized formulation.⁶⁸ This is irrespective of whether the new “equivalent medicine” is a simple

⁶⁵ Section 130a (1a) and (3a) Social Code Book 5; *Bundestagsdrucksache* 18/201, 7 sqq.

⁶⁶ Section 130a [3a] Social Code Book Five.

⁶⁷ Regulation of the *GKV-Spitzenverband* according to Section 130a (3a) Social Code Book 5, dated as of 22 October 2010; *Bundestagsdrucksache* 17/2170, 37 sqq.

⁶⁸ Act of 12 May 2011 on Reimbursement of Medicines, Foodstuffs Intended for Particular Nutritional Use and Medical Devices (Journal of Laws of 2015 item 345 as amended).

copy of the known drug for the same indication or whether it is a novel formulation, which may provide additional health benefits in areas of important patient unmet need.

2. New uses

Repurposing a known drug by identifying and testing new therapeutic uses for the product and subsequently extending the authorized therapeutic indications by the marketing authorization holder of the first use is one of the events that may trigger a re-negotiation of the price and reimbursement for this product with the relevant authorities.⁶⁹ During the re-negotiation, the authorities will most likely claim that the figures on which the original price were granted, mainly in respect of the estimated consumption, are no longer valid and will put pressure the marketing authorization holder to bring the price down. Often, when the relevant pricing authority estimates an increase in the consumption of the product due to the new indications approved, the price is likely to be reduced in order to maintain a fixed expenditure for the product. Such an approach actually discourages development of new uses for medicines that are already on the market. The marketing authorization holder is unlikely to get a premium price for the new use but the development may also trigger a price cut for the existing use.

F. Potential Solution: Differentiation by Indication

Although there are problems with the current situation, pricing and reimbursement systems also present opportunities for the reward of repurposing drugs. More advantageous pricing could be offered for products in new indications of established drugs. Again, this would require the introduction of data gathering on the use for which a drug

⁶⁹ An example is the Italian CIPE determination laying down the P&R procedure, dated 1 February 2001, article 7. In Germany it is for medicines falling under the AMNOG regime cf. Section 130b [3a] Social Code Book Five. Article 94 of the Spanish Medicinal Products Act 25/1990 and Article R163-12 of the French Code de la sécurité sociale contain similar provisions.

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is being prescribed. There could be different prices offered for
different therapeutic value.

1. An Example: Reimbursement in Belgium

Belgium operates a system whereby the list of medicinal products that are eligible for reimbursement is divided into “chapters” depending on the nature or reimbursement status of the product. For products included in chapter I, all registered indications are reimbursed, whereas the reimbursement of products included in chapter II and IV is subject to specific conditions.⁷⁰ This allows reimbursement of a given pharmaceutical to differ depending upon the use for which it is prescribed.

II. Facilitating Access to Innovation

Incentives are not the only factor to consider when analyzing the future of innovation in the pharmaceutical industry and how to encourage the development of repurposed drug products. Another important factor to consider is access to innovation. Examples of the different areas to which access needs to be improved in order to facilitate innovation are described below.

A. Access to Pipeline

Collaborations that allow exchange of information relating to industry drug portfolios and pipelines will be key to successful repurposing of known drugs going forward. Collaborations might include those between industry partners or between industry and academic institutions or governments. Collaborations, whereby industry portfolios and expertise are shared, are more likely to generate viable repurposed products. An example of such an initiative is provided by the activities of the UK-based Medical Research Council (“MRC”).⁷¹ The MRC is a non-departmental public body funded through the UK Government's science and research budget. It

⁷⁰ Art. 1, 11° of the Belgian Royal Decree of 21 December 2001 on the procedures, terms and conditions regarding the reimbursement of medicinal products.

⁷¹ More information about the MRC can be found at <http://www.mrc.ac.uk/>

has run a number of initiatives with the pharmaceutical industry that seek to harness the potential of open access to data to drive development of known drugs. GlaxoSmithKline, AstraZeneca, Pfizer, and Johnson & Johnson have all contributed experimental compounds to the public domain for development with the MRC. The compounds that have been contributed are those that have received millions of dollars of research effort from their donors but that have failed to reach the market as intended for commercial or other reasons.⁷² UK academics are to apply for MRC funding to study the compounds. The company contributing the compound would have first option on development rights to any new medicines arising from the research.⁷³

The MRC has also entered into a strategic collaboration with AstraZeneca to create a center for early drug discovery at the AstraZeneca R&D center in Cambridge, UK.⁷⁴ The idea is that MRC-sponsored researchers will work alongside AstraZeneca scientists in the screening group to “identify new methods to better understand a range of diseases and potential treatment options.” Under the scheme, AstraZeneca have granted access to over two million molecules in their compound library.

B. Access to Data and Data Mining Tools

Over the past five or so years, ease of access to data and the sophistication with which it may be manipulated and analyzed have opened the pharmaceutical industry up to new businesses, new business models, and new routes to discovery of better treatments.

There is an emerging trend towards encouraging opening up access to clinical data by policy makers in Europe. The first of January 2015 saw the entry into effect of the European Medicines Agency’s

⁷² *Id.*

⁷³ *Id.*

⁷⁴ See *AstraZeneca and MRC enter strategic collaboration to create new centre for early drug discovery in Cambridge, UK*, MEDICAL RESEARCH COUNCIL (Mar. 31, 2014), <http://www.mrc.ac.uk/news/browse/astrazeneca-and-mrc-enter-strategic-collaboration-to-create-new-centre-for-early-drug-discovery-in-cambridge-uk/>.

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clinical transparency provisions for all marketing authorization
applications submitted after that date.⁷⁵ Amongst other things, this
policy requires the proactive publication of all clinical and non-
clinical data submitted as part of the marketing authorization
application.⁷⁶ This will equate to the publication of an unprecedented
volume of data regarding drug behavior, efficacy, and safety. Anyone
wishing to access data under the scheme will be required to confirm
that such use is not for commercial purposes.⁷⁷ Nevertheless, it signals
the beginning of even greater availability of information that may lead
to better understanding and dissemination of data regarding how drugs
work. Increased understanding brings with it the potential to discover
new treatments.

There are already examples of businesses in the health care
industry that have become successful largely because of their ability
to gather and analyze data. For instance, part of the California
biotechnology company 23andMe's business⁷⁸ is providing a saliva-
based direct-to-consumer personal genome test that relies on
compiling and comparing data against a huge genome database. One
of the other parts of the business is using the large pool of data that
they have to partner with academics and industry.⁷⁹ They are even said
to be pursuing drug development themselves.⁸⁰

The example described above shows that analyses of datasets of
known drug behavior can suggest direction for further research. Such
analyses may be conducted relatively inexpensively and may
potentially open up drug discovery and development to additional

⁷⁵ For more information on the EMA's clinical trials transparency policy, see
Background to clinical data publication policy, EUROPEAN MEDICINES
AGENCY,
[http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/g
eneral_content_000556.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000556.jsp) (last visited May 23, 2016).

⁷⁶ *Id.*

⁷⁷ *Id.*

⁷⁸ See 23ANDME, <https://www.23andme.com/en-gb/> (last visited May 23, 2016).

⁷⁹ *23andMe sets stage for stronger ties with pharma*, FIERCEBIOTECH (Nov. 29,
2012, 7:43 AM), [http://www.fiercebiotech.com/story/23andme-sets-stage-
stronger-ties-pharma/2012-11-29](http://www.fiercebiotech.com/story/23andme-sets-stage-stronger-ties-pharma/2012-11-29).

⁸⁰ Forbes interview with Ann Wojcicki 23andMe's founder and CEO. See
Matthew Herper, *In Big Shift, 23andMe Will Invent Drugs Using Customer
Data*, FORBES (Mar. 12, 2015, 8:01 AM),
[http://www.forbes.com/sites/matthewherper/2015/03/12/23andme-enters-the-
drug-business-just-as-apple-changes-it/#7dc1a8992278](http://www.forbes.com/sites/matthewherper/2015/03/12/23andme-enters-the-drug-business-just-as-apple-changes-it/#7dc1a8992278).

players in the industry, and with it the potential for increased innovation and competition. Collected information on known drug mechanisms of action can drive virtual drug discovery, either in suggesting new uses for known drugs or predicting the effects of untested drugs. In the near term, the potential is clear for these sorts of analyses to suggest new uses for known drugs. Developing known drugs for new purposes in this way is particularly attractive because it brings with it the advantage of knowing that such drugs are safe, thereby bypassing the need to extensively test the safety of that product, and so shortening the development timeline; making it more predictable and lowering cost.

Until relatively recently, discovery of new uses for known drugs has often been by serendipity. Well-known and successful drug repurposings, such as Viagra, were discovered whilst testing the drugs for treatment of other unrelated disorders. “Big data” gives the potential for greater direction for this route of discovering new treatments. For example, Dr. Dakshanamurthy of Georgetown University in Washington D.C.⁸¹ has matched publically available data about the structure of drug molecules with databases of proteins found in the human body and the sort of molecules they interact with. When testing the model they found it was able in 91 percent of the 3,671 drugs tested to match a drug to a protein known to be its target.⁸² It is easy to imagine how a system with a sufficient volume of suitably specific data could create fast and reliable suggestions for alternate uses for known molecules. Indeed, the researchers showed that the system was already able to suggest avenues for possible future research, both of new uses for known products and even of molecules that have not yet been produced physically.⁸³

C. Regulatory Early Access Tools

The European Medicines Agency is making serious attempts to be able to provide swift market access for medicines using the legislative

⁸¹ See *Computers may give new life to old medicines*, THE ECONOMIST (Aug. 11, 2012), <http://www.economist.com/node/21560236>.

⁸² *Id.*

⁸³ *Id.*

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tools currently available. A pragmatic approach to regulatory assessment with shorter regulatory assessment procedures that take into account real life evidence are best suited for innovations related to new uses for old molecules. The risk to patients is greatly reduced where the product has already undergone the safety testing necessary to take the product to market. Faster regulatory access schemes would be a valuable tool in opening up the pharmaceutical industry to new entrants and increasing innovation. Shorter, cheaper, and more effective regulatory processes with reduced time to market can help to increase innovation by reducing cost and lowering the barriers to market entry.

Some examples of the ways in which the established medicine regulatory process is being adapted to provide fast, intelligent market access for novel medicinal products are described below. Overwhelmingly these processes are reserved at present for medicines that serve the most urgent and important patient need. Hopefully, some of these processes, or processes similar to them, will be available more widely in the future, and will be used to encourage market access for new medicines developed from known substances, since their known safety profiles should allow shortened research and development timelines.

1. STAMP

In 2015 the European Commission set up STAMP (the Commission Expert Group on Safe and Timely Access to Medicines for Patients).⁸⁴ The goal of STAMP is stated as being to “exchange views and information about the experience of Member States, examine national initiatives and identify ways to use the existing EU regulatory tools more effectively. The main goal is to further improve safe and timely access and availability of medicines for patients.”⁸⁵ Under active consideration by STAMP at the moment are conditional

⁸⁴ See *Early access tools: accelerated assessment and conditional marketing authorization*, EUROPEAN MEDICINES AGENCY (Oct. 15, 2015), http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/11/WC500196321.pdf and *Commission Expert Group on Safe and Timely Access to Medicines for Patients* (“STAMP”), EUROPEAN COMMISSION, http://ec.europa.eu/health/documents/pharmaceutical-committee/stamp/index_en.htm (last visited May 23 2015).

⁸⁵ *Id.*

marketing authorizations, accelerated assessment and PRIME and adaptive pathways. These alternative routes to marketing authorization operate under current EU regulatory tools.

2. Conditional Marketing Authorizations

A conditional marketing authorization is available currently in specific circumstances where the benefit-risk balance of a given product is such that the need for immediate availability of the product outweighs the limitations of having less comprehensive data than would otherwise be required to grant marketing authorization.⁸⁶ This is typically the case for products where there is a patient population with unmet medical need, seriously debilitating or life-threatening disease, a rare disease, or use in emergency situations.⁸⁷ In such cases, it is possible for the European Medicines Agency's Committee for Medicinal Products for Human Use to recommend the early approval of a marketing authorization on the basis of less complete clinical data, and subject to certain specific pharmacovigilance⁸⁸ and other data collection obligations. The granting of a conditional marketing authorization allows medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and ensures that additional data on a product are generated, submitted, assessed, and acted upon.

The Netherlands' Ministry of Health launched a project in 2011 to investigate whether it might be possible to encourage further development of known authorized medicines for treatment of new

⁸⁶ Provision for conditional marketing authorizations is made in Regulation (EC) No. 726/2004 laying down Community procedures for the authorisation and supervisions of medicinal products for human and veterinary use and establishing a European Medicines Agency and they are further defined in Regulation (EC) No. 507/2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004.

⁸⁷ *Id.*

⁸⁸ Pharmacovigilance is the term used for monitoring the effects of drugs after they have been licensed for use, especially in order to identify and evaluate previously unreported adverse reactions.

284 WASHINGTON JOURNAL OF LAW, TECHNOLOGY & ARTS [VOL 12:3 diseases, so-called “drug rediscovery.”⁸⁹ The rationale is that without some incentive, industry will not further develop known drugs. Quicker and easier routes to market may be one such incentive, in particular where there is already known off-label use of that product.

3. Accelerated Assessment

The pharmaceutical legislation contains within it provisions for “accelerated assessment procedures” to meet the “legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies.”⁹⁰ These accelerated procedures are reserved under the legislation for medicinal products of major therapeutic interest and may be requested by the applicant for authorization of such a medicine when making an application. What is meant by “major therapeutic interest” or “major public health interest” is not defined. It will be for the applicant to justify eligibility for the procedure and in particular that the medicinal product addresses to a significant extent the “unmet medical needs for maintaining and improving the health of the Community.” This will be assessed on a case-by-case basis.

4. Adaptive Licensing

The concept of adaptive licensing seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and harms. This will be done by using the existing regulatory processes within the existing EU legal framework.

Medicines Adaptive Pathways to Patients (MAPPs) or Adaptive Pathways is an EU-level initiative that seeks to provide timely and potential early access to promising medicines that address significant unmet medical needs.⁹¹ The general principle is that approval and

⁸⁹ Stimulering van Drug Rediscovery, ZonMw, The Netherlands Organisation for Health Research and Development.

⁹⁰ See Regulation No 726/2004, 2004 O.J. (L 136).

⁹¹ See *Adaptive pathways*, EUROPEAN COMMISSION, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp (last visited May 23, 2015).

reimbursement decisions are made using a more flexible framework, allowing launch of the therapy based on limited, yet clearly promising, evidence that can be expanded and assessed regularly post-launch.

A pilot scheme was started in 2014 in which the European Medicines Agency called for the involvement of real-world medicines in development.⁹² The European Medicines Agency plan to make their first report on the pilot scheme in 2016 but have already reported to STAMP on their initial experiences with it. To date, 20 candidate products have been selected for in-depth discussion of the adaptive licensing pathway with the applicant.

5. PRIME scheme (Priority Medicines)

The PRIME (PRiority Medicines) scheme is a European Medicines Agency initiative which aims to enhance early dialogue to facilitate accelerated assessment of priority medicines.⁹³ It is part of the European Medicines Agency initiative to accelerate patient access to medicines that address unmet needs. This includes the adaptive pathways pilot, the accelerated assessment, and conditional marketing authorization pathways.⁹⁴ PRIME is concurrent to those initiatives, seeking to review their impact on authorization of priority medicines. It also considers how to enhance and reinforce early dialogue and regulatory support to stimulate innovation, optimize development, and enable accelerated assessment of these medicines. As with accelerated development, conditional marketing authorizations and adaptive processing, PRIME is focused on medicines of major public health interest and within the existing regulatory framework. The

⁹² For more information about the launch of the pilot project, *see* Press Release, European Medicines Agency, European Medicines Agency launches adaptive licensing pilot project (Mar. 19, 2014), *available at* http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/03/WC500163410.pdf.

⁹³ The October 2015 EMA Reflection Paper on PRIME may be found at http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2015/10/WC500196065.pdf

⁹⁴ *Id.*

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PRIME initiative is currently under public consultation. The European Medicines Agency expects to launch PRIME in the first quarter of 2016.

6. ADAPT SMART

ADAPT SMART stands for Accelerated Development of Appropriate Patients Therapies, a Sustainable, Multi-stakeholder Approach from Research to Treatment-outcomes.⁹⁵ This is an initiative led by the European Medicines Agency and run in parallel to the adaptive pathways pilot project. The ADAPT SMART program was set up to investigate the conceptual framework that may, in the future, be used in adaptive pathways, including tools and methodologies.⁹⁶ ADAPT SMART is run by the Innovative Medicines Initiative (IMI2), the European public-private collaboration for which the European Medicines Agency is the scientific leader.⁹⁷ The aim of the ADAPT SMART initiative is to facilitate and accelerate the availability of the MAPPs pathway to authorization to all healthcare stakeholders.

D. Access to Funding

It may not be possible to encourage the development of new uses for known drugs if the funding for such research must come entirely from the pharmaceutical industry. The industry has already shown that it is willing to explore government partnerships and increased interaction with academia in order to increase development opportunities and lead to the discovery of new treatments. An example of such collaboration is the Innovative Medicines Initiative (“IMI”).⁹⁸ The IMI is Europe's largest public-private initiative, which supports

⁹⁵ For more information, see Committee For Medicinal Products for Human Use, Reflection paper on a proposal to enhance early dialogue to facilitate accelerated assessment of priority medicines (PRIME), (European Medicines Agency, Working Paper 2015) available at <http://adaptsmart.eu/adapt-smart-kick-off-meeting-the-innovative-medicines-initiatives-adapt-smart-laying-the-foundations-and-building-consensus-to-make-mapps-work-for-all>.

⁹⁶ *Id.*

⁹⁷ *Id.*

⁹⁸ See IMI, <http://www.imi.europa.eu/> (last visited May 23, 2015).

collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. It is a partnership between the European Union (represented by the European Commission) and the pharmaceutical industry (represented by EFPIA).

Launched in 2008, IMI is the world's biggest public-private partnership in the life sciences.⁹⁹ The aim of the initiative is to speed up development of, and improve patient access to, innovative medicines (particularly in areas of unmet medical or social need). The IMI invites consortia of small and medium-sized enterprises, mid-sized companies, patients' organizations, regulatory authorities, academic teams, industry, hospitals, and other organizations to respond to or generate proposals for projects that will address the challenges that affect public health. The IMI provides funding and other support for these projects.

The IMI operates a number of projects, some of which are focused on specific health issues and some of which are focused on broader challenges in drug development—such as drug/vaccine safety and the use of stem cells for drug discovery.¹⁰⁰ A number of the IMI initiatives use big data and modeling to aid treatment discovery. For example, the Pharma-Cog initiative aims to predict cognitive properties of new drug candidates for neurodegenerative diseases in early clinical development.¹⁰¹ Pharma-Cog seeks to bring together databases of previously conducted clinical trials and combine the results from blood tests, brain scans, and behavioral tests, to develop a 'signature' that will give more accurate information on the progression of the disease and the likely effect of candidate drugs than current methods.¹⁰² Alongside the modeling, studies are conducted with laboratory models, healthy volunteers, and patients in order to better predict good new drugs as early as possible.

Claimed successes of the IMI program include the generation of a line of human pancreatic beta cells (the cells which go wrong in

⁹⁹ *Id.*

¹⁰⁰ *Id.*

¹⁰¹ *Id.*

¹⁰² *Id.*

288 WASHINGTON JOURNAL OF LAW, TECHNOLOGY & ARTS [VOL 12:3 diabetes), the creation of a simple computer test that predicts if a potential drug will be harmful to the heart, and the creation of novel clinical trial designs for schizophrenia and Alzheimer's disease treatments.¹⁰³

E. Access to Patients

As the transparency requirements with respect to the industry's clinical data increases, so does patients' online access to information regarding medical conditions and treatment. European laws that prohibit advertising of prescription medicines to patients act effectively as a bar to the pharmaceutical industry discussing their treatments with patients based in the European Union.¹⁰⁴ Attempts by the European Commission to introduce new laws to increase patient access to reliable information on prescription medicines have been rejected;¹⁰⁵ the often cited concern being that changes to these laws may lead to a US-style market in which consumers are marketed to by the pharmaceutical industry rather than provided with the information with which to help them make their own decisions.

However, the lack of territorial boundaries online means that patients who want to read about treatments and share their questions and concerns will find the information somewhere. Inaccurate and untested information may thrive in an environment in which those with the most information about the treatments in question, being the pharmaceutical industry, are prevented from engaging in the discussion. New laws that may meet the objective of providing patients with the information they want and require, but that respectfully maintain a limitation on large-scale "advertising" (in the traditional sense), would be a welcome development to increasing patient focused innovation. The industry could listen actively to their customers and provide feedback with a level of understanding and

¹⁰³ *Id.*

¹⁰⁴ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to medicinal products for human use, art. 86 to 100, 2001 O.J. (L 311) 67.

¹⁰⁵ See discussion in 2008 in *Pharmaceutical Package*, EUROPEAN COMMISSION, http://ec.europa.eu/health/human-use/package_en.htm (last visited May 23, 2015).

speed that is not possible currently. It would help them understand what the patients want and may guide more patient-focused development opportunities.

F. Patent Pools

Patent pools¹⁰⁶ can facilitate drug development as they widen access to protected technology. Patentee members of a patent pool are encouraged to share their drug patents with other members of the pool. The members of the pool benefit from availability of the technology to, for example, produce the technology themselves or in some cases develop the technology without fear of being sued for patent infringement by the patentee.

An example of a patent pool is the Medicines Patent Pool (MPP), which is a United Nations-backed organization offering a public health-driven business model.¹⁰⁷ It was devised on patent pool principles and works through a system of voluntary licensing and patent pooling. The MPP aims to lower the prices of HIV, tuberculosis, hepatitis C, malaria, and tuberculosis treatments in low and middle-income countries and to facilitate the development of better-adapted medicines.¹⁰⁸ Under the MPP, patentees may be compensated by a fair royalty under a license. The MPP works with governments, industry and international organizations, as well as those communities and people affected by HIV. To date, the MPP has signed agreements for twelve antiretrovirals with six patent holders and is working with 14 manufacturers on more than 50 projects to develop HIV-licensed medicines.

G. Access for Third Party Developers

Many of the incentives that aim to encourage research and development of new drugs may actually disincentivize further

¹⁰⁶ A patent pool is formed by a group of patent owners where each agrees to cross licence patent rights to the others.

¹⁰⁷ MEDICINES PATENT POOL, <http://www.medicinespatentpool.org/> (last visited May 23, 2015).

¹⁰⁸ *Id.*

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research and development of known drugs by third parties (i.e. by anyone other than the originator of the original drug who is the compound patent owner and marketing authorization holder). Patents and market exclusivity protecting the known drug will prevent the marketing of that product by a third party even if that third party had completed studies to show that the product was effective in a different treatment area. As it stands, therefore, there is in practice very little development of known pharmaceuticals by third parties until after patent and SPC expiry. Until then, all development potential lies with the holder of the patent for the drug molecule.

An open question is whether this could be an area for further consideration. Could, perhaps, third parties that discover new uses for known medicinal products be permitted to benefit from certain carve-outs of either patent or regulatory protection over the “reference” or original product? Might provision be made for the benefit coming from the third party development to be shared between the third party and the originator? A “softer” option may be that the carveout may apply in the EU only to SPCs and regulatory exclusivities rather than the patents themselves, where the full 20-year term would have to be respected. Another alternative could hypothetically be the adaptation of the compulsory licensing provisions. Any such hypothetical regime would certainly bring with it the potential to increase the incentive for third parties to invest in further investigation of a medicinal product once it had gained its initial marketing authorization. The question would then be whether the remaining protection for the original drug innovation is still sufficient to allow for a fair return.

CONCLUSION

A system to reward the development of repurposed drugs has the potential to benefit all of the relevant stakeholders. The pharmaceutical industry would have more products coming through pipeline. Patients would be presented with greater choice of more efficacious and safer medicines, more information and certainty regarding treatment options, and more timely access to treatment. Clinicians would need to rely less on off-label treatments, would have a greater number of treatment choices, and could be more confident about the information they receive. Finally, the healthcare systems will benefit from having healthier patients that may remain contributors to society and the national economy.

A system to reward the research and development in known medicinal products is justified, but any such system must be considered carefully. The goal should be to incentivize and promote research and development that lead to new and useful treatments. It should not create monopolies over products that restrict legitimate market entry and provide disproportionate reward to trivial therapeutic advances. The ideal system of incentives would therefore offer reward relative to the size of the innovation and patient benefit and would be fairly balanced against the benefit to patients of timely generic market entry.

Building such a system requires consideration of both incentives to innovate but also how different types of access that facilitate such innovation can be improved. A meaningful framework of incentives cannot be achieved through changes to either the patent or regulatory system in isolation as they operate currently. Changes to prescribing and dispensing practices are also required: specifically a method of specifying which indication a medicine with more than one use has been prescribed for on the prescription is critical. Without knowing for what indication a medicinal product is being prescribed and dispensed, both the patent and regulatory systems lack the necessary data to be able to form the basis of a fair and enforceable system of incentives for repurposed drugs.

As well as incentives, access that facilitates innovation must also be considered. Access to drug portfolios, pipelines, and funding needs to be improved through collaboration between industry, governments, and academia. Increased access to clinical data, technology, and patients will facilitate informed and targeted drug development. Access to the market could be enhanced by the introduction of shorter and less onerous regulatory procedures for new uses for known drugs, and by allowing early market access for independently developed uses for known drugs before the expiry of exclusivity.

Finally, we need to convince payers to increase their willingness to reward the “repurposing” of known drugs. This would involve setting up appropriate procedures enabling them to assess the added value of these products as well as introducing systems of data gathering on the use for which a drug is being prescribed.

Repurposed drugs have huge potential. It is important that the systems are in place to incentivize and reward the research and

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development effort required to realize that potential. Getting the
balance right between incentivizing the development of new drugs and
encouraging the continued investigation of further possible uses for
such drugs could bring enormous benefits to all healthcare
stakeholders.¹⁰⁹

¹⁰⁹ The opinions expressed in this article are those of the author.