www.palgrave.com/journals
www.genevaassociation.org

The Geneva Papers on Risk and Insurance

Issues and Practice

Volume 48 • No. 3 • July 2023

Contents

THE GENEVA ASSOCIATION

palgrave macmillan

ISSN 1018-5895 (Print), ISSN 1468-0440 (Online)

THE GENEVA PAPERS

Vol. 48 • No. 3 • July 2023

THE GENEVA ASSOCIATION

The Geneva Papers on Risk and Insurance

Issues and Practice

www.palgrave.com/journals
www.genevaassociation.org

July 2023
Volume 48 No. 3

The Geneva Papers on Risk and Insurance—*Issues and Practice*

An official journal of The Geneva Association—
The International Association for the Study of Insurance Economics
www.palgrave.com/journals

Founded by The Geneva Association in 1976, this prestigious journal will continue to publish papers which both improve the scientific knowledge of the insurance industry and stimulate constructive dialogue between the industry and its economic and social partners. It is essential reading for academics and researchers in insurance, their colleagues in the insurance industry and other professionals who are searching for deeper insight into the strategic options for their sector. It bridges the gap between these groups, highlighting converging zones of interest and helping them to find a common direction.

The Geneva Papers is published in a combined print and online format. Fully searchable, full-text versions of all articles are available in addition to PDF. A subscription not only gives unlimited access to the current volume but also to all issues from 1976.

Submissions

All articles should be submitted electronically at: *https://www.editorialmanager.com/gpri/default.aspx* or sent to: Hannah Dean (*Editorial Manager*), The Geneva Association, Talstrasse 70, CH-8001 Zurich.
Tel. +41 44 200 49 00, Fax. +41 44 200 49 99
E-mail: genevapapers@genevaassociation.org
Print ISSN 1018-5895
Online ISSN 1468-0440

Contents

Volume 48 • No. 3 • July 2023

SPECIAL ISSUE ON EMERGING RISKS AND (LIABILITY) INSURANCE IN THE TIME OF PANDEMICS

Guest Editors: Ina Ebert, Michael Faure and Ernst Karner

This issue is now available at:
www.palgrave.com/journals

The Geneva Association

The Geneva Association is the leading international insurance think tank for strategically important insurance and risk management issues.

The Geneva Association identifies fundamental trends and strategic issues where insurance plays a substantial role or which influence the insurance sector. Through the development of research programmes, regular publications and the organisation of international meetings, The Geneva Association serves as a catalyst for progress in the understanding of risk and insurance matters and acts as an information creator and disseminator. It is the leading voice of the largest insurance groups worldwide in the dialogue with international institutions. In parallel, it advances—in economic and cultural terms—the development and application of risk management and the understanding of uncertainty in the modern economy.

The Geneva Association membership comprises a statutory maximum of 90 chief executive officers (CEOs) from the world's top insurance and reinsurance companies. It organises international expert networks and manages discussion platforms for senior insurance executives and specialists as well as policymakers, regulators and multilateral organisations.

Established in 1973, The Geneva Association, officially the International Association for the Study of Insurance Economics, is based in Zurich, Switzerland and is a non-profit organisation funded by its members.

The Geneva Papers on Risk and Insurance - Issues and Practice (2023) 48:669–686
https://doi.org/10.1057/s41288-023-00302-z

COVID-19 off-label uses of medicines: the role of civil liability and regulation

Andrea Parziale[1]

Received: 3 September 2022 / Accepted: 4 May 2023 / Published online: 19 May 2023

Abstract

Physicians can prescribe medicines for different indications than the tested and authorised ones. Such 'off-label' uses expand therapeutic options but also create uncertainties. The COVID-19 pandemic triggered new off-label uses and, despite issues being reported in the literature, these have not resulted in substantial personal injury litigation in the EU. Against this backdrop, this article argues that civil liability plays, in fact, a limited role in off-label uses. In particular, civil liability may incentivise health actors to follow and react to the development of the evidence basis for off-label uses. However, it is ultimately unable to incentivise the conduct of additional research on off-label uses. This is problematic, as off-label research is key to protecting patients and is recommended by international medical ethics. The article concludes by critically discussing proposed mechanisms to incentivise off-label research. It argues that extending civil liability for unknown risks may have undesired effects on insurability and innovation, and most regulatory proposals seem ineffective. Building on the 2014 Italian reform of off-label uses, the article proposes the establishment of a fund financed by mandatory contributions from the industry, which should be used by pharmaceutical regulators to promote off-label research and develop guidelines for prescribers.

Keywords Off-label uses of medicines · COVID-19 · Civil liability · Pharmaceutical regulation · Research incentives · EU

✉ Andrea Parziale
andrea.parziale@maastrichtuniversity.nl

[1] Institute for Transnational Legal Research, Faculty of Law, Maastricht University, Bouillonstraat 1-3, 6211LH Maastricht, The Netherlands

Introduction

Ensuring that a medicine's benefits outweigh its risks is the primary goal of pharmaceutical regulation (Goldberg 2013, p. 4). This is to ensure that only safe and effective medicines reach patients, with side effects kept to an acceptable level. Accordingly, before medicinal products are marketed, pharmaceutical regulatory frameworks require pharmaceutical companies to test their products and regulators to assess the gathered evidence (Davis and Abraham 2011). If this assessment is positive, regulators authorise the marketing of the medicinal product for the tested indication. After they are marketed, pharmaceutical companies and public regulators monitor the real-world effects of the product and take action as appropriate to inform and protect the public from emerging risks (pharmacovigilance) (Kaeding et al. 2017). The authorised indications are indicated not only in the regulatory approval document but also in the product information delivered both to physicians and patients. Uses of a medicine in line with the product-authorised indications are known as on-label uses.

When prescribing authorised products, physicians are also allowed to diverge from the terms of the respective marketing authorisation. Thus, medicines may be prescribed for indications that have not been tested by the manufacturer and assessed by regulators. Such 'unauthorised uses of authorised products' are defined as 'off-label' uses (Aronson and Ferner 2017).[1] Such uses are common and often beneficial (Beck 2021, p. 19). They are a driver of medical innovation, offering additional therapeutic options to patients that lack satisfying therapeutic alternatives (European Commission 2017a, p. 12). For example, paediatric (Allen 2018) and oncologic (Saiyed et al. 2017) diseases are frequently the object of off-label uses. Many off-label uses are long-standing in clinical practice and have proven safe and effective, with some of them even ending up being considered standard treatment (Beck 2021, p. 13).

Conversely, more innovative off-label uses tend to expose patients to higher uncertainties than on-label uses. Indeed, less comprehensive information is available on their safety and effectiveness compared to on-label uses. This is because off-label uses are generally not as thoroughly tested as the latter.

Although this does not necessarily mean that innovative off-label uses are dangerous, empirical studies do suggest that they are associated with an increased risk of unexpected adverse reactions (Eguale et al. 2016). Sometimes, off-label uses even result in mass accidents. An example of this is the U.S. Risperdal case.[2] Risperdal was approved as an antipsychotic medicine, yet it was extensively prescribed off-label to treat other conditions, including attention deficit hyperactivity disorder (ADHD). Such uses were suspected to originate numerous cases of gynecomastia (i.e. growth of male breasts). Another off-label mass accident is the French Mediator *affaire* (Einbinder 2020). Mediator was approved for diabetes but was largely prescribed off-label as a hunger suppressant. Such uses were later associated with increased cardiac risks—and possibly

[1] As such, off-label uses are radically different from compassionate uses of investigational products. These latter are exceptionally authorised uses of unauthorised products (Balasubramanian et al. 2016; Rahbari and Rahbari 2011; Zettler and Greely 2014). Conversely, off-label uses are unauthorised uses of authorised products.

[2] *Harper v Janssen Pharms., Inc*., No. 2:17-CV-603-WKW-DAB, 2018 WL 2691492, at *8 (M.D. Ala. 4 April 2018).

thousands of deaths. Following such and similar scandals, off-label uses have increasingly caught the attention of legislators and courts.

The COVID-19 pandemic sparked innovative off-label uses worldwide (Shojaei and Pooneh 2020). While some COVID-19 off-label uses showed some efficacy, the medical literature also reported issues associated with such uses (Lee et al. 2021; Ramos-Esquivel et al. 2022; Dasgupta 2021; Shojaei and Salari 2020). However, this has not resulted in major off-label personal injury litigation.

Against this backdrop, this paper focuses on the conditions for establishing civil liability in relation to off-label uses, as well as on gaps and potential ways to fill them. To this end, this paper is structured as follows. First, some context is provided by discussing COVID-19 off-label uses and regulatory reactions to them in the U.S. and EU. Secondly, ethical and legal frameworks for off-label uses are outlined to identify the main actors involved as well as their respective duties and responsibilities. Thirdly, the relationship between civil liability and off-label uses is discussed. Subsequently, the potential impact and limitations of civil liability in relation to off-label uses is assessed. Finally, also based on a critical discussion of past proposals, a (regulatory) proposal is put forward to address the identified limitations without undermining insurability and innovation in the pharmaceutical sector.

Off-label uses and the COVID-19 pandemic

The COVID-19 outbreak led to new off-label uses, although presumably with different levels of prevalence across countries. Given the lack of products specifically tested and approved for COVID-19, uses of medicines to treat COVID-19 patients are, by definition, off-label (Shojaei and Salari 2020). Examples include the use of medicines authorised for the treatment of malaria (Chloroquine, Hydroxychloroquine and Amodiaquine), bacterial infections (Azithromycin), Ebola (Remdesivir), influenza (Favipiravir, Umifenovir, Oseltamivir and Ribavirin), HIV (Ritonavir/Lopinavir), fibrosis (Nafamostat and Camostat), arthritis (Tocilizumab), parasite infestations (Ivermectin and Nitazoxanide), ulcers (Famotidine) and inflammation (Corticosteroids and Dexamethason) (Neupane et al. 2021; Pawar 2020).

In the face of COVID-19 off-label prescriptions in clinical practice, the overall approach followed by U.S. and EU regulators was to try to balance the need to speed up access to treatment and the need to protect public health (Parziale 2022, pp. 65–66). First, regulators strove to strengthen the monitoring of such uses, also by promoting observational studies on the real-world effects of COVID-19 off-label uses. Secondly, based on safety reports and the results of observational studies, regulators provided recommendations for physicians to use or not use specific off-label uses for COVID-19 treatment. U.S. and EU regulators used different regulatory tools to this end, particularly emergency use authorisations and recommendations, respectively. Finally, regulators tried to bring off-label uses on-label, e.g. by facilitating large-scale clinical trials.

Against this backdrop, calls for protecting physicians from liability were also addressed to lawmakers on both sides of the Atlantic (Grey and Orwoll 2021). Despite being common to the U.S. and the EU, however, such calls had very different results in each jurisdiction. In the U.S., wide liability immunity was

implemented, with injured parties being allowed to request a limited indemnity from the *Countermeasures Injury Compensation Program*, which is funded by general taxation (Whelan 2022). Some scholars pointed out that the radical shield from liability adopted in the U.S. was mostly unnecessary (Grey and Orwoll 2021, p. 84). In their view, the common law already 'lowers the bar' of the standard of care in situations of emergency. In other terms, common law adequately protects healthcare professionals and manufacturers from liability claims. What is more, these scholars claimed that liability immunities might even prove counterproductive. Behind such liability shields, operators may lose incentive to follow the ever-evolving basis of scientific evidence underpinning off-label prescriptions, and this may result in increased risks of patient harm (Grey and Orwoll 2021, p. 72).

In the EU, proposals for extensive liability immunity were not adopted.[3] However, widespread off-label personal injury litigation did not materialise either. This is despite the fact that the literature reported severe issues with COVID-19 off-label uses. These include evidence of substantial incidence of adverse reactions (Lee et al. 2021), high prevalence of potential drug-drug interactions (Ramos-Esquivel et al. 2022), lack of effectiveness (Dasgupta 2021) and forms of pseudo-research (Shojaei and Salari 2020).[4] The lack of substantial off-label personal injury litigation is even more puzzling considering that, in several EU jurisdictions, health-related litigation is generally far from uncommon. An explanation for this may be that in times of emergency, patients are more proactive and tend to accept higher risks in exchange for the chance of having their condition treated. Thus, they may be more reluctant to sue physicians and manufacturers afterwards.

Another potential reason (not necessarily alternative to the previous one) is that civil liability plays a limited role in off-label uses of medicines. This calls for a clarification of the conditions that may warrant civil liability in relation to such uses.

Ethics and regulation of off-label prescribing

Before addressing the relationship between civil liability and off-label uses, a brief recap of the ethical-legal framework for such uses is needed. This allows the identification of the main actors involved, as well as their respective duties and responsibilities. Both are relevant to off-label personal injury litigation.

As anticipated in the introduction, 'off-label' is just a regulatory term. The mere lack of testing and regulatory authorisation does not say anything about the benefit-risk profile of a specific medicinal product (Beck and Azari 1998, p. 81). Nevertheless, innovative off-label uses tend to be associated with an increased level of scientific uncertainty compared to on-label uses. Off-label uses may, indeed, expose

[3] Although discussions on this are not uncommon in the European literature (Cioffi and Rinaldi 2020; Tozzo et al. 2020; Bilotta et al. 2020).

[4] These consist of "using off-label medications in clinical practice without obtaining the patient's informed consent, and finally publishing the results of drug efficacy as a research article" (Shojaei and Salari 2020). Off-label uses may ultimately discourage patients.

patients in clinical practice to uncertainties that resemble those of an experimental context. In other words, they involve a 'grey area', blurring the boundaries between medical research and clinical practice. This is highlighted also by the U.S. Belmont Report, a key international reference document regarding the distinction between treatment and research (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978).

These concerns lie at the core of international medical ethics recommendations applicable to off-label uses. For instance, Paragraph 37 of the Helsinki Declaration provides physicians with several recommendations when it comes to an unproven intervention (World Medical Association 2013). These include recommendations to ensure that such unproven intervention offers hope to improve the patient's health status; seek expert advice; obtain the patient's informed consent; closely monitor the patient; conduct research on the unproven use; and share the results, as appropriate. This arrangement broadly underlies most regulatory approaches in the EU.

At the outset, EU case-law holds that off-label prescribing is generally admitted,[5] adverse reactions to it must be reported via the pharmacovigilance system (which has been made explicit by Directive 2010/84 and Regulation 1235/2010), and off-label promotion is prohibited (European Commission 2017, pp. 17–18). At the national level, a number of EU member states consider off-label prescriptions as mostly a matter for physicians' professional judgment, and do not foresee specific policy tools for them (European Commission 2017, pp. 60–61). Nevertheless, an increasing number of EU member states are adopting more specific regulatory frameworks (Lenk and Duttge 2014). Most of these focus on reimbursement policies, since the reimbursement of medicines used off-label may be cost-saving for National Health Systems (European Commission 2017, p. 58).[6]

Other EU member states feature comparatively more comprehensive regulatory frameworks (European Commission 2017a, 2017b). Italy and France provide prominent examples of this approach. In particular, the Italian legislation on off-label uses (Law 94/1998, as amended) states that off-label prescriptions are only permitted in individual cases, under the physician's direct responsibility, if all the following conditions are met: the informed consent of the patient is acquired; the treating physician has estimated that specifically approved medicines cannot usefully treat the specific condition of the patient; the off-label uses have been reported in internationally recognised scientific publications (and supported by favourable results of completed phase II trials, as specified by Article 2(348), Law 244/2007). This legislation originated from the so-called *Di Bella* treatment *affaire* of 1997–1998, which consisted of an off-label cocktail of medicines, vitamins and hormones that Dr Di Bella claimed were able to cure cancer. This treatment was not supported by the scientific community and was ultimately disproved (Guidi et al. 2021).

[5] European Court of Justice, case C-535/11, *Novartis Pharma GmbH v Apozyt GmbH* [2013] EU:C:2013:226, paragraph 48.

[6] For instance, the medicine prescribed off-label for a specific indication is cheaper than the medicine specifically authorised for that same indication. The *Avastin-Lucentis* saga (Arnaudo 2014; Dyer 2020) provides an example of this.

Under French legislation, as amended effective 1 July 2021, off-label uses aimed to meet a patient's 'special needs' fall under the scope of the so-called *cadre de prescription compassionnelle* (L. 5121–12-1 *Code de la santé publique*). This framework enables the French pharmaceutical regulator to streamline the reimbursement and pharmacovigilance of off-label uses. This legislation replaced the *recommendations temporaires d'utilisations*, which had been introduced to address the weaknesses of the French pharmacovigilance system unveiled by the Mediator (benfluorex) *affaire* (Emmerich et al. 2012).

This summary of the ethical-legal framework for off-label uses suggests that off-label prescribing is not only a matter of interest for patients and healthcare professionals, but also for manufacturers and regulators alike. In addition, it outlines the main duties and responsibilities of each health actor, although with different focuses and levels of detail. Medical ethics focuses on the requirements of a legitimate off-label use in terms of necessity, scientific rationale, patient-informed consent, as well as monitoring, research and data sharing. Safety regulations focus, instead, on the pharmacovigilance duties of manufacturers and regulators, which are required to react in a timely manner to emerging risks. As will be seen in more detail below, civil liability can fine tune some, but not all, of these key duties and convey incentives to discharge them.

Off-label civil liability in the EU

Starting with medical liability, courts generally assess whether the off-label prescription meets the general principles of medical diligence (Aagaard and Kristensen 2018). These essentially require the physician to:

(i) Ensure that the unauthorised use is based on scientific data, with varying degrees of specificity across jurisdictions, ranging from 'acquired' scientific evidence in France to evidence from internationally recognised scientific literature and completed phase II trial data in Italy. However, if the off-label use in question is common clinical practice, physicians may use this argument to rule out their professional liability,[7] leaving it to the claimant to show that such off-label use was, nonetheless, faulty.

(ii) Ensure that the benefit-risk ratio for the individual patient is positive. This implies that the physician (a) should not prescribe off-label if an effective on-label prescription option is available and (b) should closely monitor the effect of the treatment on the patient.[8]

[7] This seems to have been quite common in French Mediator-related litigation (Prescrire 2020).

[8] The Italian *Corte di Cassazione* applied these principles in a decision given in 2008 regarding a physician who prescribed a medicine for acne and hirsutism, which resulted in the patient's death from hepatitis caused by the medicine's toxicity. The court found the physician at fault for prescribing a highly toxic medicine for a non-severe condition and for failing to monitor the patient's liver condition during treatment (Cassazione, Judgment of 13 March 2008, no. 17499, in Il Foro italiano 7–8, no. II (2008): p. 376). "If a drug is used in the case of a disease for which it is not sufficiently tested, an increased level of caution (especially regarding the dose) and monitoring must be shown to be aware of warning signals and to be able to react immediately" (Lenk and Duttge 2014).

(iii) Acquire the patient's informed consent. In particular, physicians are generally not required to disclose to the patient that the prescription is off-label, with the notable exception of France (Guidi et al. 2021).

(iv) Provide a causal link between the prescriber's conduct and the injury. Similar to other litigation areas, courts do not always require conclusive scientific evidence for the claimant to show causation and may admit proof by presumptions, based on a discussion of the available evidence and a consideration of alternative causal factors in the individual case (Parziale 2022, p. 113; Steel 2015; Goldberg 1999).

Besides medical liability, manufacturer liability under Directive 85/374/EEC (Product Liability Directive, PLD) may also come into play. Contrary to the U.S., product liability litigation is scarce in the EU. However, the French Mediator litigation provides an interesting case study (Jourdain 2016), with the caveat that the conclusions reached by the French courts are not automatically relevant to other EU jurisdictions (despite product liability being, in principle, harmonised). Below is a general discussion of the peculiarities posed by off-label uses relative to EU product liability law in general. The Mediator case law is mentioned for the limited purpose of showing how French courts addressed such peculiarities.

First, the manufacturer's liability cannot necessarily be excluded on grounds that the product was prescribed to the patient by a third party (i.e. the treating physician) outside the terms of the product authorisation. Indeed, Article 6 PLD states that a product is considered defective if it does not meet the safety expectations of the public considering all circumstances, including "the use to which it could reasonably be expected that the product would be put" (Article 6(1)(b) PLD). This notion of reasonably expected use likely covers off-label uses that have become widespread in clinical practice and known or reasonably knowable to the manufacturer. By applying product liability to a widely common and known medicinal off-label use, the French Mediator case law seems to support this argument.

Second, the question arises if and to what extent a medicinal product, the off-label use of which is harmful, can be considered defective. As is well known, under the PLD, a product is considered defective "when it does not provide the safety which a person is entitled to expect". This notion of defect is argued to rely on an objective consumer safety expectations test (Verheyen 2019, pp. 45–46). In *Boston Scientific*,[9] the Court of Justice of the EU (CJEU) refined this definition of defect by stating that safety expectations can be particularly high for some products. For these, if products belonging to the same batch have a potential defect, any product belonging to that same batch can be considered defective. This is despite the fact that it is not proven that the product in question actually has a defect. While *Boston Scientific* concerned a pacemaker and cardioverter defibrillator, it can be argued that such high safety expectations may be expected from pharmaceuticals as well.

[9] CJEU, Judgment of 5 March 2015, C-503/13, Boston Scientific Medizintechnik GmbH v AOK Sachsen-Anhalt—Die Gesundheitskasse, EU:C:2015:148.

Thus, the PLD does not explicitly embrace the U.S. tripartite doctrine of information/warning, design and manufacturing defects. However, the influence of this terminology is present in European PL case law (Wuyts 2014), and scholars debate over the compatibility of each defect type with the PLD safety expectations test.

The least problematic defect type is the information or warning defect. This is because information and warnings about product use directly shape consumer safety expectations. Indeed, this is the most common ground for pharmaceutical product liability claims in general. This likely applies to off-label use claims as well, since pharmacovigilance obligations also cover such uses. In particular, French courts held the Mediator manufacturer liable under the PLD for the injuries caused by the off-label use of the product. This is because the manufacturer failed to react in a timely manner to the increased cardiac risks associated with such use after evidence had emerged in the literature that could not be neglected.

Other kinds of product defect are design and manufacturing defects. While the former relies on a risk-utility assessment of the product (Verheyen 2019, p. 45), the latter may materialise when the product is not produced according to its design (id. 51). The admissibility of such defect types under Article 6 PLD is a matter of controversy in the legal scholarship (Wuyts 2014). In any event, they may be relevant for off-label cases in those jurisdictions that admit them. For instance, some Mediator-related decisions held that the increased cardiac risks associated with the off-label use of the product warranted a design defect.[10] However, when the risks associated with off-label uses are less severe, a manufacturer might argue that such risks do not undermine the product overall risk-utility ratio, if its on-label uses are perfectly safe and effective. Manufacturing defects may also come into the picture. However, such defects are not expected to pose peculiarities specific to off-label uses, as they may typically impair consumer safety expectations, irrespective of whether the product is used on- or off-label.

Third, the PLD requires the claimant to show causation between product defect and injury. This task may prove daunting in scientifically complex and uncertain matters, such as those related to pharmaceutical PL. This is, naturally, approached quite differently across the EU. Some countries, like France and Italy, tend to adopt a rather liberal approach to proof of causation (Alpa 2019), which may be proven 'by presumptions' that are 'serious, specific and consistent'. Proof of causation of this kind may, therefore, in principle be reached, even with a lack of conclusive scientific evidence and formally validated rates of probability. For instance, regarding off-label product liability specifically, French courts established causation in Mediator cases based on 'acquired' scientific evidence, indicating a causal link between product use and injury, as well as on the fact that, in the specific instances considered, alternative causal explanations were unavailable.[11]

[10] Cassation, 1ère civile, Judgment of 20 September 2017, 16–19.643, JURITEXT000035612653; Cassation, 1ère civile, Judgment of 25 February 2016, 15–11.257, JURITEXT000032120145.

[11] Cassation 1ère civile, 22 May 2008, no. 05–20.317, JURITEXT000018868809; Cassation 1ère civile, 22 May 2008, 06–10.967, JURITEXT000018868823.

Proving product defect, injury and a causal link between the two is, in principle, sufficient for the claimant to recover damages under the PLD. Nevertheless, the manufacturer may still escape liability by invoking one of the exemptions listed in Article 7 PLD. In pharmaceutical PL cases, one of the most relevant exemptions is the so-called development risk (or unknown risk) defence (Article 7(e) PLD). This defence enables the manufacturer to avoid liability if they demonstrate that the state of scientific and technical knowledge at the time the product was put into circulation did not allow discovery of the defect. Adverse reactions to off-label prescriptions may easily fall under its scope, given the scientific uncertainty that generally surrounds their effects.

Naturally, much depends on how the wording of Article 7(e) PLD is interpreted. The CJEU did clarify that the 'state of scientific and technical knowledge' relevant to the exemption is to be considered the 'most advanced knowledge' in the field, rather than majority opinion.[12] However, the notion of 'most advanced knowledge' is, in turn, not clearly defined. A restrictive interpretation is that the 'most advanced knowledge' is only that relying on scientifically certain data (Comandé 2013). A consequence of this is that the manufacturer can escape liability by showing that, at the time of product supply, the defect was not yet scientifically established. This is regardless of the fact that, at that time, non-conclusive data were available that were indicative of the product defect. Under this restrictive interpretive approach, unexpected adverse reactions to off-label uses would unlikely warrant product liability.

An alternative interpretation of 'most advanced knowledge' is that it includes non-conclusive yet plausible data about the product defect as well (*ibid.*). Therefore, if such evidence is available at the time of product supply, then the manufacturer cannot successfully invoke the development risk defence. This may result in at least some unexpected side effects falling under the scope of product liability. A broader interpretation of this kind seems more in line with the proactive approach conveyed by the pharmacovigilance framework, which requires companies (alongside regulators) to act to protect the public before a risk is formally established, along the line of the precautionary principle. Indeed, in the Mediator case law, French courts adopted quite a restrictive reading of the development risk defence. In particular, the *Cour de Cassation* held that a product defect can be considered discoverable once the harmful effects of products with a similar chemical composition and metabolic action have been revealed and regulators abroad have withdrawn the product based on pharmacovigilance reports and international studies.[13] Thus, the court rejected the manufacturer's

[12] CJEU, Judgment of 29 May 1997, C-300/95, Commission of the European Communities v United Kingdom, EU:C:1997:255.

[13] Cassation 1ère civile, 22 November 2017, 16–23.804 16–24.719, JURITEXT000036090492.

argument that, by the time the product was marketed, the defect could not be discovered considering the state of scientific and technical knowledge.[14]

Finally, alongside pharmaceutical companies, regulators play an important role in pharmacovigilance, also with respect to off-label uses. Shortcomings in this respect may, in principle, warrant a form of state civil liability. This is because pharmaceutical regulators are usually set up as state agencies. Approaches to state liability, however, vary significantly across the EU, France and Italy being jurisdictions where public health authorities have been held liable in connection to severe scandals.[15] Therefore, it should not come as a surprise that the French Mediator litigation showed that regulators might also be held liable in relation to off-label uses. In particular, the *Conseil d'État*[16] held that, since the late 1990s, the French pharmaceutical regulator negligently failed to fulfil its pharmacovigilance obligations (Petit 2014). By 1999, the court argued, evidence had emerged that 'could not be neglected' about the correlation between Mediator and increased cardiac risks. Such evidence was provided by international studies and regulatory decisions and information was explicitly discussed within the French pharmaceutical regulatory body. Nevertheless, the French pharmaceutical regulator informed patients about such risks only in 2009.

Interestingly, the Mediator case law addressed the relationship between the different kinds of civil liability. Overall, French courts recognised that the civil liability of the different health actors can, indeed, concur either as joint and several liability (for instance, between a negligent physician and the manufacturer) or separate liability (as in the case of state liability, for reasons of procedural law). The pre-existing conditions of the victim were sometimes accounted for to reduce the amount of damage awards.[17] Conversely, courts generally did not find a comparative fault (or contributory negligence, in the common law language) of victims. In principle, it could be argued that the fact that the patient consented to the treatment could at least warrant a reduction of the damage award. This kind of 'victim's fault' was generally not found, likely because patients are not considered, to use a U.S. legal expression, 'experts in the field'. This means that a layperson cannot reasonably be expected to be aware of the scientific debate on the risks of medical prescriptions. Physicians and manufacturers, on the other hand, can.

[14] It is noteworthy that French law has a divergent implementation of the development risk defence. The latter does not apply to human body parts or derivatives (Article 1245–11, *Code Civil*, previously Article 1386–12). This may be relevant to off-label uses of products containing such peculiar substances. In contrast, I disagree with the view that the 10-year limitation period foreseen by Article 1245–15, *Code Civil* (previously Article 1386–11) implies a substantial change in the scope of the development risk defence (Fondazione Rosselli 2004, p. 30). This limitation period merely means that product liability cannot be invoked 10 years after the product was put into circulation, unless a claimant filed a lawsuit before. This does not directly intefere, per se, with the scope of the development risk defence.

[15] For instance, the infected blood scandal, see Cassazione sezioni unite civili, Judgment of 11 January 2008, no. 576, in Giustizia Civile 11, no. I (2009): 2577 and Conseil d'État, Judgment of 9 April 1993, no. 138653, CETATEXT000007839300.

[16] Conseil d'État, 9 November 2016, no. 393108, CETATEXT000033387533.

[17] Cassation, 1ère civile, 20 September 2017, 16–19.643, JURITEXT000035612653.

Importantly, to facilitate victim compensation, the French state set up a specific, publicly funded Mediator fund under the framework of the ONIAM amicable settlement system (Legoux 2016). In essence, based on victims' dossiers, a multidisciplinary board either recommends the insurer of the relevant health actor to formulate a compensation offer, or, if no civil liability seems warranted, requests the fund to indemnify the victim. The insurer can refuse to comply. In this case, the state compensates the victim and has subrogation rights towards the insurer. If this redress action is successful, the insurer may be required to refund the state plus pay an extra penalty. Thus, both the victim and the insurer can go to court, but a system of subrogation rights and penalties strengthens incentives to make offers and settle.

The role and limitations of civil liability

It follows from the above that civil liability seems to play a limited role vis-à-vis off-label uses. In particular, civil liability rules are likely to apply the most blatant cases of harmful off-label uses, i.e. when the off-label use is, at the outset, either not necessary, lacks a scientific rationale or when the treatment is continued despite the occurrence of a suspected adverse reaction.

Conversely, civil liability does not seem to provide adequate protection against the off-label uses that are most insidious for public health. Suppose, for instance, that an off-label use first seems needed and scientifically justified, and for these reasons becomes common clinical practice. Suppose also that, after quite some time, such an off-label use turns out to be harmful in light of new available evidence, with numerous patients ending up injured. In these cases, as already stated, patients injured after the emergence of a new risk may be entitled to recover from the relevant health actors on grounds of medical negligence, product liability or negligent pharmacovigilance. Conversely, patients injured before the emergence of the new risk are unlikely to be able to recover from any of the actors involved. This is because, generally, unknown risks do not warrant fault-based liability (since the very notion of fault is strictly linked to that of risk foreseeability) or product liability (since state-of-the-art or development risk defences tend to apply).

A first consequence of this is that wide civil liability immunity is probably not justified, even in an emergency context. Physicians, manufacturers and regulators cannot be held liable for unknown risks associated with a specific off-label use. Suppose that, at the time of the prescription the latter was necessary and scientifically sound, the patient being fully informed about all known benefits, risks and uncertainties. In this case, civil liability can hardly be warranted for any of the health actors concerned.

An additional consequence is that civil liability may convey incentives to the health actors concerned to monitor patients, follow the development of the evidence basis for off-label uses, and react accordingly. This falls along the lines of key basic tenets of the ethical-legal framework for off-label uses. Complementing this, regulators should facilitate this by sharing recommendations on off-label uses primarily aimed at supporting prescribers' decision-making processes that are in line with the most updated scientific evidence (Guidi et al. 2021).

On the other hand, lack of liability for unknown risks means that the current civil liability framework for off-label uses is not well suited to incentivise additional research (and particularly randomised clinical trials (RCTs), as the golden standard for generating reliable evidence) to discover new risks regarding off-label uses in the first place. This is compatible with literature findings that off-label uses are generally not sufficiently studied (Dresser 2009). A major factor behind this is arguably that pharmaceutical companies do not have particular economic incentives to conduct research on off-label uses, which multiply the potential uses of a specific medicine and its sales volumes without having to undergo lengthy and costly testing and approval procedures (Rusz et al. 2021; Verbaanderd et al. 2020). Lack of research on off-label uses is also more detrimental in pandemic times as "[i]n addition to the risk of harming patients without the possibility to even detect the magnitude of harm, the administration of off-label drug use, compassionate drug use, and uncontrolled studies during a pandemic also could discourage patients and clinicians from participating in RCTs, hampering any knowledge that could be gained about the effects of the drug being tested" (Kalil 2020).

Therefore, lack of sufficient research on off-label uses is a critical issue that calls for appropriate solutions. Indeed, producing knowledge and reducing uncertainties regarding off-label uses is key to protecting public and patients' health and is recommended by international ethics as well, such as paragraph 37 of the Helsinki Declaration and the Belmont Report.

More research, fewer uncertainties: a critical discussion of scholarly and policy proposals, and the potential way forward

In sum, civil liability may incentivise health actors to follow and react to new knowledge regarding off-label uses, but not to produce such new knowledge in the first place. This is problematic, because improving knowledge and reducing uncertainties on off-label uses is key to protecting patients, especially when it comes to off-label uses that are no longer isolated but start spreading in clinical practice.

To promote research on off-label uses, the literature has already put forward several proposals. Some argue that research incentives may be conveyed by imposing an outright strict liability regime (Rodwin 2014). Alternatively, a tort law duty to conduct research to discover new risks could be construed (so that, for instance, if a patient is injured by a risk that was unknown at the time of the accident, the manufacturer may be held liable for not having researched the product or identified the risk in question) (Sila 2018).

Both proposals warrant forms of civil liability for unknown risks. This is, however, problematic (Faure et al. 2016). This is because liability for unknown risks is difficult to insure and may have negative effects on innovation. Both are critical concerns in a key economic sector of larger societal importance, such as the pharmaceutical sector.

In fact, regulation may be better suited than liability to promote off-label research without undermining insurability and innovation. Several regulatory proposals have already been put forward. Some focus on incentivising companies to test off-label

uses, with a view to applying for marketing authorisation extensions (in sum, to bring off-label uses on-label) (Verbaanderd et al. 2020). To this end, it is suggested that the EU should provide companies with additional data and marketing protection periods or grant priority review for future marketing authorisation applications (*ibid.*). Alternatively, country-specific incentives, such as tax incentives, may be offered (Nayroles 2017). Another approach could be to reduce current disincentives for the pharmaceutical industry to apply for marketing authorisation extensions through fee reductions or waivers for scientific advice or variation applications (Verbaanderd et al. 2020, p. 7). This could be complemented with streamlining the identification of repurposing opportunities and accelerating the clinical uptake of repurposed medicines (id. 8). Broadly along these lines falls the repurposing strategy outlined in the European Medicines Agency (EMA) 2025 strategy (EMA 2020). The latter focuses on enhancing scientific and regulatory advice on evidence generation and marketing authorisation application submission, as well as on promoting real-world data collection (EMA 2020).

While these proposals may prove useful to facilitate off-label research, the fundamental limitation of most of them is that they do not address the fact that companies ultimately lack economic or financial interest to do research on off-label uses in the first place. The industry already profits from off-label uses, so to say, by default. Therefore, cheaper approval and scientific advice procedures and more or less generous tax breaks for research can arguably do little to induce them to invest in further research on off-label uses. In this respect, the experience of the old French framework for *Recommendations temporaires d'utilisations* (RTUs) is quite telling. RTUs aimed, among other things, to incentivise pharmaceutical companies to conduct tests on off-label uses of their products with a view to applying for an extension of the marketing authorisation (Degrassat-Théas et al. 2015). However, RTUs proved unable to deliver this outcome and were eventually repealed.

For the same reason, the industry can hardly be expected to voluntarily fund independent research, e.g. by academic or not-for-profit institutes. This is, indeed, a typical example of market failure. In more explicit terms, the industry does not fund third-party research because this produces positive externalities (the research outcome), which, as a public good, the industry can appropriate for free. This, in turn, results in the public good not being produced in the first place.

As is often argued in the face of such market failures, 'government provision' of the under-produced public good (in this case, research on off-label uses) would be justified. However, this proposal needs to be duly qualified. First, not all off-label uses should be researched (which would be inefficient), but only those for which a specific public interest exists. Competent regulatory agencies would be best placed to identify the off-label uses that meet this requirement. In any event, these would reasonably include off-label uses that address unmet medical needs and that are no longer isolated and start spreading in clinical practice. Researching off-label uses to fight a pandemic would likely be in the public interest as well. In addition, the costs of off-label research should be borne not by general taxation, but rather by the industry, as it profits directly from the sales of the products that are being used off-label.

The Italian Law-Decree no. 36/2014 outlined a regulatory mechanism that broadly fell along these lines. Under Article 3(1) of the mentioned Law-Decree, in

cases of justified public interest, the Italian Medicines Agency (*Agenzia Italiana del Farmaco*, AIFA) could apply for the registration of an off-label use (and, therefore, conduct clinical trials), relying on a fund financed by compulsory contributions from the industry. This was subject to the marketing authorisation holder (MAH) transferring the rights regarding such a use to the Ministry of Health for free. The marketing authorisation holder of the product concerned could apply for the registration of the off-label use themselves, agreeing with AIFA on the timeline and methodology of the clinical trials. However, under the last sentence of Article 3(1) of the mentioned Law-Decree, the MAH could object to AIFA registering the off-label use, thus effectively preempting this whole mechanism. If the objection was without reason, then a merely 'reputational' sanction applied, consisting of a notice on AIFA's website.

Lacking proper sanctions, this regulatory framework proved ineffective and was promptly repealed when the Law-Decree was converted into law shortly after (Article 1, Law no. 79/2014). However, it provides a compelling model to promote off-label research that, almost 10 years later, has not yet received the attention it deserves in the literature and policy debate.

Naturally, the pharmaceutical industry would likely strongly lobby against mechanisms of this kind. However, advocacy initiatives by patient and physician organisations, possibly teaming up with competent regulatory authorities as well, have the potential to draw legislators' attention towards them. An updated regulatory framework of this kind should, in any event, provide not only for effective sanctions against unjustified lack of collaboration by the industry. Mechanisms should also be foreseen to facilitate the involvement of academic and not-for-profit institutes (to promote independent research and minimise conflicts of interest), as well as to account for public health emergencies. Importantly, the competent regulatory authority should be tasked with using research outcomes to develop guidelines to support prescribers' decision-making in clinical practice.

Conclusions

The COVID-19 pandemic promoted new off-label uses of medicines. Despite several issues being reported in the literature, these have not resulted in substantial personal injury litigation. In the U.S., this is the direct result of wide liability immunities. In the EU, this may be indicative of the limited role civil liability plays in relation to off-label uses. In particular, this article argued that civil liability can provide protection against the most blatant cases of harmful off-label uses, but not those that are most dangerous to public health. These include off-label uses that first seem beneficial and spread in clinical practice, only to turn out to be harmful. A consequence of this is that civil liability can incentivise health actors to follow and react to the development of the evidence basis for an off-label use, but not to do research on it in the first place. Since off-label research is key to reducing uncertainties and protecting patients and is recommended by international ethics, appropriate solutions are needed. Extending civil liability to unknown risks may convey incentives to carry out additional research, but may undermine insurability and innovation in a sector of critical societal importance. Regulatory frameworks may offer more balanced

solutions. However, they risk remaining ineffective if based on voluntary and incentivising mechanisms alone. As a more effective solution, this article proposes that governments should set up off-label research funds, financed by compulsory contributions from the industry, which regulatory agencies could use to conduct research on off-label uses in the public interest. The 2014 Italian (temporary) framework provides an interesting case study to support advocacy initiatives by patient and physician organisations.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

Aagaard, L., and K. Kristensen. 2018. Off-label and unlicensed prescribing in Europe: Implications for patients' informed consent and liability. *International Journal of Clinical Pharmacy* 40 (3): 509–512. https://doi.org/10.1007/s11096-018-0646-4.

Allen, H.C., M.C. Garbe, J. Lees, N. Aziz, H. Chaaban, J.L. Miller, P. Johnson, and S. DeLeon. 2018. Off-label medication use in children, more common than we think: A systematic review of the literature. *The Journal of the Oklahoma State Medical Association* 111 (8): 776–783.

Alpa, G. 2019. General remarks on civil liability in the European context. *European Business Law Review* 2019: 101–116.

Arnaudo, L. 2014. The strange case of Dr. Lucentis and Mr. Avastin. The Italian Competition Authority Fines Roche and Novartis for Collusion. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.2428126.

Aronson, J.K., and R.E. Ferner. 2017. Unlicensed and off-label uses of medicines: Definitions and clarification of terminology. *British Journal of Clinical Pharmacology* 83 (12): 2615–2625. https://doi.org/10.1111/bcp.13394.

Balasubramanian, G., et al. 2016. An overview of Compassionate Use Programs in the European Union member states. *Intractable & Rare Diseases Research* 5 (4): 244–254. https://doi.org/10.5582/irdr.2016.01054.673.

Beck, J.M. 2021. 'Off-label use in the twenty-first century: Most myths and misconceptions mitigated. *UIC John Marshall Law Review* 54 (1): 27.

Beck, J.M., and E.D. Azari. 1998. FDA, Off-label use, and informed consent: Debunking myths and misconceptions. *Food and Drug Law Journal* 53 (1): 71–104.

Bilotta, C., S. Zerbo, G. Perrone, G. Malta, and A. Argo. 2020. The medico-legal implications in medical malpractice claims during Covid-19 pandemic: Increase or trend reversal? *Medico-Legal Journal* 88 (1_suppl): 35–37. https://doi.org/10.1177/0025817220926925.

Cioffi, A., and R. Rinaldi. 2020. Covid-19 and medical liability: A delicate balance. *Medico-Legal JOurnal* 88 (4): 187–188. https://doi.org/10.1177/0025817220935879.

Comandé, G. 2013. La responsabilità civile per danno da prodotto difettoso…assunta con 'precauzione. *Danno e Responsabilità* 1: 107–112.

Dasgupta, N. 2021. Safety Consequences of Off-Label Drugs Used for COVID-19. *Drug Safety* 44 (4): 399-402. https://doi.org/10.1007/s40264-021-01056-0.

Davis, C., and J. Abraham. 2011. A comparative analysis of risk management strategies in European Union and United States pharmaceutical regulation'. *Health, Risk & Society* 13 (5): 413–431. https://doi.org/10.1080/13698575.2011.596191.

Degrassat-Théas, A., F. Bocquet, M. Sinègre, J. Peigné, and P. Paubel. 2015. The "Temporary Recommendations for Use": A dual-purpose regulatory framework for off-label drug use in France. *Health Policy* 119 (11): 1399–1405.

Dresser, R., and J. Frader. 2009. Off-label prescribing: a call for heightened professional and government oversight. *Journal of Law, Medicine & Ethics* 37 (3): 476–486. https://doi.org/10.1111/j.1748-720X.2009.00408.x.

Dyer, C. 2020. Offering Avastin for wet AMD is legal, says appeal court. *BMJ*. https://doi.org/10.1136/bmj.m1273.

Eguale, T., D.L. Buckeridge, A. Verma, N.E. Winslade, A. Benedetti, J.A. Hanley, and R. Tamblyn. 2016. Association of off-label drug use and adverse drug events in an adult population. *JAMA Internal Medicine* 176 (1): 55–63. https://doi.org/10.1001/jamainternmed.2015.6058.

Einbinder, F. 2020. Mass Torts: Dispute resolution in France and the United States–the Vioxx and mediator cases compared. *Washington International Law Journal* 29: 575–648.

EMA. 2020. Regulatory Science to 2025 Strategic reflection. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf

Emmerich, J., N. Dumarcet, and A. Lorence. 2012. France's new framework for regulating off-label drug use. *New England Journal of Medicine* 367 (14): 1279–1281. https://doi.org/10.1056/NEJMp1208347.

European Commission and Directorate-General for Environment. 2017. The precautionary principle: Decision-making under uncertainty. *Publications Office*. https://doi.org/10.2779/947379.

European Commission Directorate-General for Health and Food Safety. 2017. Study on off-label use of medicinal products in the European Union: Report. *Publications Office*. https://doi.org/10.2875/464022.

Faure, M., L. Visscher, and F. Weber. 2016. Liability for unknown risks—A law and economics perspective. *Journal of European Tort Law*. https://doi.org/10.1515/jetl-2016-0010.

Fondazione Rosselli. 2004. *Analysis of the Economic Impact of the Development Risk Clause as provided by Directive 85/374/EEC on Liability for Defective Products*. https://ec.europa.eu/docsroom/documents/7104?locale=en.

Goldberg, R. 1999. *Causation and risk in the law of torts: Scientific evidence and medicinal product liability*. Oxford: Hart.

Goldberg, R. 2013. *Medicinal product liability and regulation*. Oxford: Bloomsbury.

Grey, B.J. and S. Orwoll. 2021. Tort Immunity in the Pandemic. *Indiana Law Journal* 96 (5): 66-88. https://www.repository.law.indiana.edu/ilj/vol96/iss5/3.

Guidi, B., A. Parziale, L. Nocco, A. Maiese, R. La Russa, M. Di Paolo, and E. Turillazzi. 2021. Regulating pediatric off-label uses of medicines in the EU and USA: Challenges and potential solutions. *International Journal of Clinical Pharmacy*. https://doi.org/10.1007/s11096-021-01303-5.

Jourdain, P. 2016. Le Mediator devant la Cour de cassation: appréciation des conditions relatives à la causalité et à la défectuosité du médicament. *Revue Trimestrielle Droit Civil* 386.

Kaeding, M., J. Schmälter, and C. Klika. 2017. *Pharmacovigilance in the European Union*. *Pharmacovigilance in the European Union: Practical Implementation across Member States*. https://doi.org/10.1007/978-3-658-17276-3.

Kalil, A.C. 2020. Treating COVID-19—Off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA* 323 (19): 1897–1898. https://doi.org/10.1001/jama.2020.4742.

Lee, J.Y., et al. 2021. Incidence of adverse reaction of drugs used in COVID-19 management: A retrospective, observational study. *Journal of Pharmaceutical Policy and Practice* 14: 84. https://doi.org/10.1186/s40545-021-00370-3.

Legoux, A. 2016. Indemnisation des accidents sériels de santé publique: l'exemple du Mediator. *Gazette Du Palais* 29: 12–15.

Lenk, C., and G. Duttge. 2014. Ethical and legal framework and regulation for off-label use: European perspective. *Therapeutics and Clinical Risk Management* 10: 537–546. https://doi.org/10.2147/TCRM.S40232.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1978. *The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research*. Bethesda: The Commission.

Nayroles, G., et al. 2017. Unlocking the potential of established products: Toward new incentives rewarding innovation in Europe. *Journal of Market Access & Health Policy* 5 (1): 1298190. https://doi.org/10.1080/20016689.2017.1298190.

Neupane, P.N., K. Aman Das, K.A. Singh, and A. Verma. 2021. Off label medication to combat COVID-19: Review results to date. *The World's First International Journal Dedicated to Coronaviruses* 2 (4): 496–506. https://doi.org/10.2174/2666796701999200729145342.

Parziale, A. 2022. *The law of off-label uses of medicines: Regulation and litigation in the EU, UK and USA*. Abingdon: Routledge.

Pawar, A.Y. 2020. Combating devastating COVID-19 by drug repurposing. *International Journal of Antimicrobial Agents* 56 (2): 105984. https://doi.org/10.1016/j.ijantimicag.2020.105984.

Petit, J. 2014. L'affaire du Mediator: La responsabilité de l'État. *Revue Française De Droit Administratif* 6: 1193.

Prescrire. 2020. La quasi-totalité des prescripteurs de Mediator épargnés par les conséquences juridiques. *Revue Prescrire* 40 (438): 304–305.

Ramos-Esquivel, A., C. Fernández, L. Garro-Zamora, A.V. Chaves, and A. Viquez-Jaikel. 2022. High Prevalence of Potential Drug-Drug Interactions Among Patients Treated with Off-label Therapies for COVID-19. *Journal of Pharmaceutical Care* 10 (2): 44-47. https://doi.org/10.18502/jpc.v10i2.9972.

Rahbari, M., and N.N. Rahbari. 2011. Compassionate use of medicinal products in Europe: Current status and perspectives. *Bulletin of the World Health Organization* 89 (3): 163.

Rodwin, M.A. 2014. Compensating pharmaceutical injuries in the absence of fault. *Food and Drug Law Journal* 69 (3): 447–472.

Rusz, C.-M., B.E. Ősz, G. Jîtcă, A. Miklos, M.G. Bătrînu, and S. Imre. 2021. Off-label medication: From a simple concept to complex practical aspects. *International Journal of Environmental Research & Public Health* 18 (19): 10447. https://doi.org/10.3390/ijerph181910447.

Saiyed, M.M., P.S. Ong, and L. Chew. 2017. Off-label drug use in oncology: A systematic review of literature. *Journal of Clinical Pharmacy and Therapeutics* 42 (3): 251–258. https://doi.org/10.1111/jcpt.12507.

Shojaei, A., and P. Salari. 2020. COVID-19 and off label use of drugs: An ethical viewpoint. *DARU Journal of Pharmaceutical Sciences* 28 (2): 789–793. https://doi.org/10.1007/s40199-020-00351-y.

Sila, R. 2018. Incentivizing pharmaceutical testing in an age of off-label promotion. *New York University Law Review* 93: 941.

Steel, S. 2015. *Proof of causation in tort law*. Cambridge: Cambridge University Press.

Tozzo, P., C. Politi, A. Gabbin, and L. Caenazzo. 2020. To take care of those on the front line against Covid-19: Is it possible to limit medical liability? *Science & Justice* 60 (4): 311–312. https://doi.org/10.1016/j.scijus.2020.05.001.

Verbaanderd, C., I. Rooman, L. Meheus, and I. Huys. 2020. On-label or off-label? Overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients. *Frontiers in Pharmacology* 10: 1664. https://doi.org/10.3389/fphar.2019.01664.

Verheyen, T. 2019. Modern theories of product warnings and European Product Liability Law. *Utrecht Law Review* 15 (3): 44–56. https://doi.org/10.36633/ulr.541.

Whelan, A.M. 2022. The PREP Act and the Countermeasures Injury Compensation Program: Past, present, and future. *DePaul Law Review* 71: 689.

World Medical Association. 2013. Declaration of Helsinki: Ethical principles for medical research involving human subjects. *JAMA* 310 (20): 2191–2194. https://doi.org/10.1001/jama.

Wuyts, D. 2014. The product liability directive—More than two decades of defective products in Europe. *Journal of European Tort Law* 5 (1): 1–34. https://doi.org/10.1515/jetl-2014-0001.

Zettler, P.J., and H.T. Greely. 2014. The strange allure of state "right-to-try" laws. *JAMA Internal Medicine* 174 (12): 1885–1886. https://doi.org/10.1001/jamainternmed.2014.5767.

About the author

Andrea Parziale is a Marie Skłodowska-Curie Fellow at the Institute for Transnational Legal Research at the Faculty of Law, Maastricht University. He obtained his PhD in Law from the Sant'Anna School of Advanced Studies (Pisa, Italy) in 2019. Based on his doctoral research, he authored the monograph *The Law of Off-label Uses of Medicines: Regulation and Litigation in the EU, UK and USA* (Routledge, 2022).