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Pharmacoepidemiology and the Law

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The law describes the basic rules under which people live in modern society. Tort law, for example, provides a system of corrective justice and a coherent set of principles to decide whether a person deserves compensation for an injury he or she sustained. As another example, contract law provides a structure for adjudicating agreements between parties. In both cases, the existence of governing law helps influence the way people act. In the case of tort law, knowledge about its liability rules should incentivize people to take care to prevent accidents from happening.

In their daily work, pharmacoepidemiologists encounter many different aspects of the law. Perhaps the most recognizable connection occurs when patients seek redress in tort law for adverse effects from a medical product. In such circumstances, pharmacoepidemiologic studies may provide the scientific underpinning for the claim as to the association between the drug and the claimed outcome. Often, pharmacoepidemiologists are called as expert witnesses to interpret scientific findings for judges and juries. Other basic legal principles may also have important effects on the practice of pharmacoepidemiology. For example, pharmacoepidemiologists must navigate contract law when they develop research agreements with funding sources or owners of databases. Pharmacoepidemiologists interface with property law when they attempt to secure ownership rights over their discoveries using patents (a type of "intellectual property").

This chapter outlines three of the most recognizable intersections of pharmacoepidemiology and the law: tort law, contract law, and intellectual property law. The chapter defines and describes basic legal rules in these subject areas, and uses these rules as a basis for additional discussion about practical and ethical implications for pharmacoepidemiology. In each example, US law is used as the paradigm, with some attention to alternative models in Europe. Since much of the discussion is based on principles that are generally similar in other comparable legal systems, the lessons are applicable to pharmacoepidemiologists around the world.

Tort Law and Product Liability Lawsuits

Product liability lawsuits provide an opportunity for individuals harmed by a drug to seek damages from its manufacturer. Recent widely

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reported cases have included the nonsteroidal anti-inflammatory drug (NSAID) rofecoxib (Vioxx®), the antidepressant paroxetine (Paxil®) and other selective serotonin reuptake inhibitors (SSRIs), olanzapine (Zyprexa®) and other atypical antipsychotics, the cholesterol-lowering agent cerivastatin (Baycol®), the antidiabetic/anti-inflammatory troglitazone (Rezulin®), and the serotoninergic anorectic drug dexfenfluramine (Redux®). In this chapter, we will review how product liability lawsuits are adjudicated according to some common law principles. A basic understanding of product liability law is essential for pharmacoepidemiologists, even for those who might never find themselves in a courtroom, because such lawsuits also exert substantial influence on the field. Tort litigation brought by government agencies and individual patients can help uncover previously unavailable data on adverse effects, questionable practices by manufacturers, and flaws in drug regulatory systems [1].

The Legal Theory of Product Liability

In the centuries-old common law tradition of England, which forms the basis for legal systems in the US and a number of other countries, a consumer injured by a defective or contaminated pharmaceutical product was not permitted a right of action unless the consumer purchased the preparation directly from the manufacturer. The emergence of product liability law altered that state of affairs, permitting consumers harmed by the many products sold widely in interstate commerce and through distributors like pharmacies to seek redress for their injuries from the original manufacturers [2]. Originally, product liability was grounded in the theory of negligence, which meant that defendants would be liable for causing plaintiffs' injuries if the defendants engaged in wrongful or unreasonable conduct, even if it was unintentional. To succeed in a claim for negligence, plaintiffs needed to show (i) that defendants had a duty to exercise reasonable care; (ii) that defendants' conduct diverged from customary practices that would be followed by other manufacturers or members of the industry; (iii) that there was a causal link between the defendants' lack of care and the outcome at issue; and (iv) that the preceding three factors led to damages.

However, negligence theory did not allow enough deserving plaintiffs to be compensated for product-related injuries they suffered, particularly in cases in which products were hazardous or dangerous. Judges rationalized that some products contained an inherent risk of harm, so manufacturers that chose to sell such products needed to bear the responsibility when the products caused injury. As a result, starting in the early 1960s, judges started applying the theory of strict liability to certain product liability cases. Strict liability merely requires demonstration that the dangerous product caused the injury; as distinguished from negligence, the question is moot as to whether the defendants followed customary practices or exercised reasonable precautions. This principle permitted plaintiffs to seek compensation for injuries merely because the product was designed a certain way, irrespective of other mitigating factors. For example, the product could have a "manufacturing defect," meaning that the product did not comply with the manufacturer's own standards, or a "design defect," meaning that the product was designed in a way that conferred inherently unreasonable risk for the consumer.

Strict product liability grew quickly in popularity. In 1965, US legal scholars proposed a consensus understanding of the area in the influential Restatement (Second) of Torts, finding that a seller of a product that is "in a defective condition unreasonably dangerous to the user or consumer" should be strictly liable even if the seller "exercised all possible care in the preparation and sale of the product" [3]. Notably, the authors commented that warnings could be employed to prevent any product from being deemed "unreasonably dangerous," although

such warnings needed to address risks that the seller "has knowledge, or by application of reasonable, developed human skill and foresight should have knowledge" [4]. Thus, strict product liability also allowed plaintiffs to bring causes of action against manufacturers based on inadequate warnings, otherwise known as a "failure to warn."

Some courts were hesitant to apply strict product liability to cases emerging from the pharmaceutical field. This reticence was reflected in the Restatement, which included an important annotation relevant to prescription drugs. In Comment k to this section of the document, the Restatement noted that a pharmaceutical product "properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous" [5]. Thus, the Restatement excluded most prescription drugs from strict liability based on manufacturer or design defects. The authors separated pharmaceutical products from other products because they believed the marketing and use of pharmaceutical products "are fully justified, notwithstanding the unavoidable high degree of risk which they involve." Prominent legal scholar William Prosser summed up the justification for treating prescription drugs differently:

> The argument that industries producing potentially dangerous products should make good the harm, distribute it by liability insurance, and add the cost to the price of the product, encounters reason for pause, when we consider that two of the greatest medical boons to the human race, penicillin and cortisone, both have their dangerous side effects, and that drug companies might well have been deterred from producing and selling them. Thus far the courts have tended to hold the manufacturer to a high standard of care in preparing and testing drugs of unknown potentiality and in giving warning; but in the absence of evidence that this standard has not been met, they have refused to hold the maker liable for unforeseeable harm. [6]

Ultimately, a minority of US courts have implemented the Comment k principle and offered pharmaceutical manufacturers a blanket protection from strict liability for manufacturer or design defect claims [7]. The majority of courts charted a slightly different course. For example, in New Jersey, the state Supreme Court declined to adopt Comment k in the case of an infant who suffered severe tooth discoloration after being prescribed demeclocycline (Declomycin®), a tetracycline antibiotic. The court ruled that the Comment k shield should only apply to drugs that were "more vital to the public health and human survival than others," while less useful drugs would continue to be evaluated under strict liability [8].

In 1997, the Restatement (Third) of Torts: Product Liability tried to clarify the question about liability for design defects. It reemphasized that judicial risk–utility analysis was improper, arguing that a drug cannot be considered to have a design defect if "reasonable health care providers, knowing of such foreseeable risks and therapeutic benefits" prescribed the drug to the patient [9].

Even in jurisdictions amenable to strict product liability for pharmaceuticals, the vast majority of drugs approved by the US Food and Drug Administration (FDA) are likely to meet courts' balancing test. As a result, when a person is injured by a prescription drug, a "design defect" lawsuit based on the claim that the product was avoidably unsafe is very unlikely to succeed. Rather, plaintiffs usually seek to demonstrate "failure to warn" by the manufacturer about the adverse event at issue (nominally a strict liability claim). Alternatively, plaintiffs could sue based on a negligence theory that the manufacturer failed to take reasonable care in marketing its product, an analysis that also largely hinges on the appropriateness of the accompanying warnings. Practically speaking, the ultimate

disposition of a case filed under a strict liability failure to warn or negligence theory turns on the question of whether the warning is reasonable [10]. After these historical twists and turns in legal theory in this area, the claim for "failure to warn" has become the most common basis for litigation over pharmaceutical products. In the next section, we will review the link between the work of pharmacoepidemiologists and failure-to-warn claims.

Failure-to-Warn Claims

Whether based on strict liability or negligence, a failure-to-warn product liability action includes three main contentions: (i) knowledge of the drug risk by the manufacturer; (ii) improper warning of the drug risk; and (iii) causation of damages.

Knowledge of the Drug Risk by the Manufacturer

First, the plaintiff must demonstrate that a pharmaceutical manufacturer knew, or should have known, of the risk. Apart from the rare case decided based on a strict liability design defect, a manufacturer of a pharmaceutical product is not held accountable for risks about which it could not have known. For example, in one case, a plaintiff brought a lawsuit claiming that her oral contraceptive medication led to her having a cerebrovascular accident, or stroke [11]. The court remarked, "Dates are thus vitally important as there is no duty to warn of unknown or unforeseeable risks, and the question is whether the risk was knowable or reasonably foreseeable at the time when the plaintiff was still taking the drug." The jury found that the particular risk the plaintiff claimed could not have been known at the time the drug was prescribed, based in part on the testimony of the expert pharmacoepidemiologist who reported that "new techniques to measure these clotting effects had not then been developed" at the time of the injury. According to the court, "The warnings contained in the package inserts were adequate or … the statements contained therein were a fair representation of the medical and scientific knowledge available at the time the drug was taken by the plaintiff."

Knowledge can be actual or constructive. *Actual knowledge* is defined as literal awareness. Actual knowledge can be demonstrated by showing that the manufacturer was cognizant of reasonable information suggesting a particular risk that it did not pass on to consumers, for example when a defendant possesses data about relevant adverse events that were not disclosed. In the case of SSRIs used to treat depression, various manufacturers were found to have conducted clinical trials that showed an increased risk of suicidal ideation in adolescent patients taking the drug. Plaintiffs brought lawsuits charging that these findings were knowingly delayed for lengthy periods of time, not released, or the concerns not fairly represented [12]. For example, the largest study of paroxetine (Paxil®) in pediatric patients was conducted in the US from 1993 to 1996; it showed no benefit of the drug over placebo and 5 cases (out of 93) of suicidal ideation, as compared to 1 case out of 89 in the placebo arm and 1 case out of 95 in the comparator (non-SSRI) arm. The manufacturer, GlaxoSmithKline, allegedly sought to "effectively manage the dissemination of these data in order to minimize any potential negative commercial impact" [13]. To support this contention, plaintiffs pointed to the fact that the data were only presented in abstract form in 1998 and published in 2001 (when the authors concluded that the drug was "generally well tolerated and effective for major depression in adolescents") [14]. After the full data from this trial and others like it were made public, a new FDA health advisory in 2004 warned physicians to carefully monitor patients for "clinical worsening, as well as agitation, irritability, suicidality, and unusual changes in behavior" and emphasized that only the SSRI fluoxetine

(Prozac®) had been approved to treat pediatric major depressive disorder [15].

Constructive knowledge is sometimes called "legal knowledge," because it is knowledge that the law assumes should be present, even if it is not. Constructive knowledge is knowledge that a person did not have, but could have acquired by the exercise of reasonable care. For example, the cholesterol-lowering drug cerivastatin (Baycol®) was removed from the market in 2001 after it was linked to cases of rhabdomyolysis, a potentially fatal kidney disease. The manufacturer, Bayer, was found to possess several reports from as early as 1999 suggesting a 10-fold risk of rhabdomyolysis relative to other medications in its class, but it allegedly did not process these reports and pass them along to patients or regulators [16]. A memorandum from a Bayer official stated, "If the FDA asks for bad news, we have to give [it], but if we don't have it, we can't give it to them" [17]. In this case, Bayer could be said to have constructive knowledge of these concerns by 1999, because the company should have processed the reports and acted on them. In other cases, plaintiffs have tried to prove constructive knowledge by arguing that manufacturers should have performed different or additional analyses to better understand an important side effect of their product. The standard for constructive knowledge in these situations has been what a reasonably prudent company with expertise in this area would have undertaken.

Improper Warning of the Drug Risk

If a manufacturer has the duty to provide a warning about adverse events associated with its product, then the next question is whether an adequate warning was provided. A proper warning has certain hallmarks, including relevance, timeliness, and accuracy.

First, a warning about an adverse effect must be commensurate with the scope and extent of dangers associated with the drug. In the case of troglitazone (Rezulin®), an oral hypoglycemic approved in the US in 1997 and used by diabetic patients, the company was accused of minimizing its presentation of liver toxicity in its warning materials [18]. Elevations of hepatic enzymes in early testing were initially depicted in the descriptions of adverse effects simply as "≥3-fold." Yet, some were apparently more than 20-fold; several of those patients suffered acute liver failure. In the subsequent litigation, it was alleged that the warning was deficient because company did not initially acknowledge this clinically important difference [19].

Secondly, warnings must not be subject to undue delay. Some delays may be internal. In the case of rosiglitazone (Avandia®), another oral hypoglycemic drug, a 2007 meta-analysis linked the drug to life-threatening cardiovascular adverse events [20]. However, after a review of internal company documents, a US Senate Finance Committee report suggested that the manufacturer knew about these risks years before this article was published, but delayed warning about them and sought to limit their dissemination [21]. A primary question in lawsuits arising from the use of rosiglitazone is whether these tactics inappropriately delayed reasonable warnings about the adverse effect. Sometimes, interactions with regulators may cause delays. For example, cisapride (Propulsid®) was a pro-kinetic agent linked to potentially fatal cardiac side effects. It was reported that the manufacturer and the FDA negotiated for five years over the details of how to change the drug's label to include adverse event data that had been submitted to the agency but not made fully available to the public [22].

Thirdly, warnings must be of appropriately urgent tone. In the case of rofecoxib (Vioxx®), a new type of NSAID used for arthritis, preapproval clinical trials suggested enhanced risk of serious cardiovascular side effects, a result consistent with a later pivotal manufacturer-sponsored trial comparing the drug to naproxen, another older NSAID, in a population of patients with rheumatoid arthritis (but no

known cardiovascular disease) [23]. When the drug's official FDA label was updated in 2002 to account for these findings, subsequent lawsuits alleged that the warning was insufficiently urgent because the risk of cardiovascular events was described in vague terms and placed in the less prominent "precautions" section of the labeling [24].

Finally, a manufacturer's duty does not end with the initial warning, because it must keep up with emerging scientific data and patient reports, and warn of new side effects discovered after initial approval. In one case, plaintiffs brought a suit contending that their daughter's serious birth defects were related to a teratogenic progesterone formulation (Delalutin®) manufactured by the defendant. The court noted that the drug manufacturer is under a "continuous duty … to keep abreast of scientific developments touching upon the manufacturer's product and to notify the medical profession of any additional side effects discovered from its use" [25]. The plaintiff's expert medical witness testified that there was "sufficient scientific information and literature relative to progesterones" at the time the drug was used to "make a prudent drug manufacturer do teratogenicity studies on any progesterone agent" [25].

Causation of Damages

Another major issue in a pharmaceutical product liability case is whether the product at issue actually caused the alleged injury. Pharmacoepidemiologists may be most comfortable thinking about causation from a medical or scientific point of view. Scientists generally posit hypotheses to explain particular outcomes and then test those hypotheses by studying whether variations in the outcomes exist across populations. However, legal causation usually requires a clear causal chain from exposure to outcome, in an individual. The legal standard for causation is therefore challenged by product liability cases, in which probabilistic evidence (i.e., P values or confidence intervals) often links drugs to injuries [26]. Courts must address two types of legal causation: general and specific causation.

General causation addresses whether a product *can* cause a particular injury in the population of patients like the plaintiff. The common law standard to prove general causation is that a particular product "more likely than not" caused the damages. Some courts have held that legal causation must be demonstrated by more than an association and a mere possibility of causation, even though causal hypotheses based on such considerations are common in the scientific literature. A few courts have even gone further and defined "more likely than not" as having a relative risk of greater than 2.0, no matter how tight the confidence intervals are around a statistically significant finding of association between 1.0 and 2.0 [27]. Presumably this is based on the calculation of attributable risk in the exposed group exceeding 50%, when the relative risk exceeds 2.0. This standard has been replicated in the Federal Judicial Center's *Reference Manual on Scientific Evidence* [28] and employed in some cases to exclude epidemiologic evidence with weaker associations. For example, in the case of the antinausea drug pyridoxine/doxylamine (Bendectin®), which was claimed to be causally linked with birth defects, one court noted, "In terms of statistical proof … plaintiffs must establish not just that their mothers' ingestion of Bendectin increased somewhat the likelihood of birth defects, but that it more than doubled it – only then can it be said that Bendectin is more likely than not the source of their injury" [29]. In one case related to litigation over the link between silicone breast implants and inflammatory disease, a court excluded a study linking the product and the outcome with a relative risk of 1.24, noting that the finding was "so significantly close to 1.0" that the study "was not worth serious consideration for proving causation" [30].

However, all courts do not adhere rigidly to the 2.0 relative risk principle for general causation.

Both clinical trials and epidemiologic studies of the product at issue can establish general causation between a pharmaceutical product and an outcome. Animal studies, meta-analyses, case reports/case series, and secondary source materials (such as internal company documents) have been used in court as they are in the medical field – to help support establishing a causal link. Since pharmacoepidemiologic studies tend to assess the presence of an association, rather than directly addressing causation, courts sometimes apply the Bradford Hill criteria to connect an association with general causation (see Table 9.1 and Chapter 1).

To demonstrate *specific causation*, a plaintiff must show that the product in question caused the alleged injury in the plaintiff. This can be a particularly complex issue for pharmaceutical products. In some cases, like instantaneous allergic reactions, the causal link between a product and an outcome is clear. For more subacute or later-onset responses, however, specific causation may be hard to demonstrate. For example, in one case against Merck brought by a plaintiff who suffered a myocardial infarction shortly after starting rofecoxib, the manufacturer argued that the outcome was attributable to the plaintiff's prior existing coronary artery disease. The plaintiff countered with the fact that he was in a state of stable cardiovascular health prior to initiation of rofecoxib, that he simultaneously developed two coronary artery clots after the drug's initiation (a rare presentation for ischemic heart disease), and that many studies have confirmed the link between rofecoxib and cardiovascular disease (a point relevant to general causation) [31]. While the trial court held for the plaintiff, the decision was reversed on appeal; the appeals court ruled that, "although plaintiffs were not required to establish specific causation in terms of medical certainty, nor to conclusively exclude every other reasonable hypothesis, because [the plaintiff's] preexisting cardiovascular disease was another plausible cause of his death, the plaintiffs were required to offer evidence excluding that cause with *reasonable certainty*" [32].

Another important aspect of specific causation is that the plaintiff must demonstrate that the inadequate warnings about the adverse effect were relevant to the plaintiff's receiving the drug. If a defendant can demonstrate that even an adequate warning would have made no difference in the decision to prescribe the drug, or to monitor the patient postprescription, the case may be dismissed for lack of a proximate cause.

Table 9.1 Bradford Hill criteria.

1)	Strength of association
2)	Consistency and replication of findings
3)	Specificity with respect to both the substance and injury at issue
4)	Temporal relationship
5)	Biological gradient and evidence of a dose–response relationship
6)	Plausibility
7)	Coherence
8)	Experimental removal of exposure
9)	Consideration of alternative explanation

Source: Adapted from Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; **58**: 295–300. Reproduced with permission of SAGE Publications.

Learned Intermediary Defense

If a plaintiff successfully argues these issues and demonstrates a *prima facie* case of product liability based on a failure to warn, the manufacturer has a few possible defenses. The most relevant in the field of pharmaceutical law is the learned intermediary defense.

Originally, product liability law imposed on all manufacturers a duty to warn consumers about the risks of their products. However, starting in the 1960s, pharmaceutical manufacturers argued that it would be more effective for them to warn physicians, the gatekeepers of prescription

medicines [33]. Courts accepted that physicians' advanced training and direct contact with patients put them in an optimal position to understand and relay complex information about possible side effects. Physicians are also well placed to discuss risks and benefits applicable to particular clinical circumstances in their patients. The "learned intermediary" rule allows pharmaceutical manufacturers to fulfill their duty to warn by providing an accurate and adequate warning to prescribing physicians [34].

The implications of the learned intermediary defense are that the debates in plaintiffs' cases tend to focus on the propriety of the warning vis-à-vis the physician, rather than the patient. Therefore, warnings do not have to be offered about risks that should be obvious or are generally known to skilled medical practitioners [35]. However, when the information given to physicians omits, underemphasizes, misstates, or obfuscates dangers, this deficiency is legally transferred to the patient, who maintains a right of redress against the manufacturer if those dangers materialize and cause injury.

If the manufacturer imparts an appropriate warning to physicians, then the manufacturer can be insulated from liability. In such cases, the focus of the litigation then often turns to the conduct of the physician and the physician–patient interaction. For example, in one case a lawsuit was brought following the suicide of a patient who had been prescribed two antihypertensive drugs, hydrochlorothiazide (HCTZ) and reserpine (Harmonyl®). The label for HCTZ stated that it might "potentiate the action of other antihypertensive drugs," while the insert for reserpine stated that the drug should be discontinued at any sign of "despondence" and that there were reports of drug-related depression severe enough to result in suicide. Because the physician was presumed to have had constructive knowledge of both of these warnings, the court insulated the manufacturers from liability [36].

In special situations, pharmaceutical manufacturers may lose the ability to invoke the learned intermediary defense. If a manufacturer markets its product very aggressively and without sufficient attention to certain risks, courts may rule that it has essentially undone the physician–patient prescribing relationship. Direct-to-consumer advertising (DTCA) is one modality that can undercut the assumption that patients are largely ignorant of prescription drug risks and that manufacturers lack means of interacting with patients other than through physicians. DTCA is currently only permitted in two industrialized countries around the world: the US and New Zealand. The New Jersey Supreme Court has ruled that DTCA created a limited exception to the learned intermediary defense [37], and in 2007 the West Virginia Supreme Court rejected the learned intermediary defense in its entirety on this basis [38]. Nonetheless, in most jurisdictions, the learned intermediary rule still stands.

Expertise and *Daubert*

Pharmacoepidemiologists often serve as expert witnesses in product liability cases. Pharmacoepidemiologists can help judges and juries understand data about drugs and help determine whether warning information appropriately reflects the risk posed by a drug. Experts are usually called on to describe the current state of knowledge about the adverse event at issue, and may be asked to perform additional pharmacoepidemiologic analyses of available data to present before the court.

However, courts can exclude some practitioners and some analyses from trial. Traditionally, the judge is responsible for evaluating whether expert witnesses lack qualifications or espouse scientific theories out of step with accepted knowledge [39]. In the 1993 case of *Daubert v. Merrell Dow*, the US Supreme Court outlined a number of criteria for reviewing the appropriateness of expert witness testimony, including whether the theory was current and whether it had been tested or subjected to peer review and publication [40]. A subsequent case applied these

rules and further refined them in evaluating a debate over the admissibility of expert testimony suggesting that polychlorinated biphenyls (PCBs) can cause lung cancer. The research was excluded because the experts did not validate their conclusions: the epidemiologic studies did not report a statistically significant causal link between PCBs and lung cancer, lacked proper controls, and examined substances other than PCBs [41]. As federal circuit court judge Richard Posner has explained in separate circumstances, "the courtroom is not the place for scientific guesswork, even of the inspired sort" [42].

In the US, some state courts have embraced the *Daubert* guidelines, which have also been taken up by revised Federal Rules of Evidence [43]; others adhere to an alternative doctrine that excludes testimony containing theories that do not enjoy "general acceptance in the relevant scientific community" [44]. Thus, pharmacoepidemiologists seeking to present expert evidence in litigation will routinely face judicial inquiry to determine whether they are fit to serve in that role. Judicial oversight in general sets a low floor for reliable expert testimony, although it can be expected to exclude experts who lack the relevant qualifications, lack facts to back up their perspectives, lack reliable methods, or fail to apply the methods appropriately [45]. There is considerable skepticism about the effectiveness of courts as a gatekeeper for expert witnesses, with some commentators citing judges' lack of the technical knowledge needed to meaningfully evaluate medical and scientific expertise [46].

The Effect of Regulation on Product Liability Litigation in the US

In the last few years, there has been a wave of controversy about the role of government regulation of pharmaceuticals in product liability claims against drug manufacturers. Under the US Food, Drug, and Cosmetic Act, originally passed in 1938, the FDA is required to certify that prescription drugs are safe enough and show efficacy for their intended indication before being sold on the US market [47] (see also Chapters 1 and 8). At the time of approval, the FDA also endorses the official drug labeling, which presents a description of the basis for the drug's efficacy as well as safety concerns that have emerged during the preapproval testing [48]. The labeling, which is generally written by the manufacturer and approved by the FDA, has legal significance as well. For example, because the FDA restricts certain types of manufacturer communication about non-FDA-approved (or "off-label") indications, the label determines what a pharmaceutical manufacturer can communicate to physicians and the public about its product [49]. The FDA requires the manufacturer to mention important warnings that are in the official labeling when marketing its product, but does not require manufacturers to mention warnings that are not in the labeling.

For most of its history, the FDA has regulated the drugs sold in the US without any direct role in product liability litigation brought by consumers injured by FDA-approved drugs [50]. The agency's noninterventionist posture changed for the first time in September 2002 in a product liability case brought after a man was prescribed the SSRI sertraline (Zoloft®) and started experiencing agitation, confusion, and suicidal thinking, ultimately leading him to take his own life one week later [51]. The plaintiffs claimed that the manufacturer failed to warn appropriately about the risks of suicide. The manufacturer contended that such a claim could not be brought because the FDA had not included such a warning in the official label, and the Supremacy Clause of the US Constitution preempts states from imposing legal requirements (in this case, via a tort action in state court) that directly contradict federal law [52]. Driven by the political preferences of its leadership at the time, the FDA filed an amicus brief in

the case on behalf of the defendant manufacturer, arguing that imposition of product liability would "undermine the agency's authority to protect the public health" [53]. The brief claimed that an adverse court ruling would force companies to add warnings not approved by the FDA and could upset the delicate benefit/risk balancing that went into the construction of the drug labeling, which could result in overwarning and ultimately underuse of an effective drug.

The major deficiency in the logic of those favoring FDA preemption in this area is that these arguments inappropriately regard the FDA's official label as the final word on drug safety. In fact, preapproval clinical trials necessarily involve only a limited sample of patients and are often powered to detect changes in efficacy-related endpoints, rather than rates of adverse events (see Chapter 4). The FDA will not have a complete picture of the safety of drugs, even at the time the labeling is written. After approval, the FDA lacks the resources and capability to actively monitor evolving knowledge about a drug [54]. Until the FDA Amendments Act (FDAAA) of 2007 (Public Law 110-85), the FDA had no authority to compel manufacturers to update the warnings in drug labeling. After the withdrawal of rofecoxib, Sandra Kweder, Deputy Director of the FDA's Office of New Drugs, said in testimony at a US Senate hearing, "We don't have the authority to tell a company, 'This is how your label has to look. This is the language that needs to go into your label. Here is where it goes, end of story.' We have to negotiate with the company the specific language of how things should be worded, the placement, those kinds of things" [55]. The FDAAA gave the FDA limited authority to "require" labeling changes "if the Secretary becomes aware of new safety information that the Secretary believes should be included in the labeling of the drug," but made these decisions reviewable through an alternative dispute resolution procedure [56]. Although this new authority strengthened the FDA's hand somewhat, ensuring compliance can still involve a lengthy and resource-intensive legal process. While the pathway established by FDAAA has rarely been publicly invoked in the decade since passage of the law, its existence may strengthen the FDA's position in its negotiations with manufacturers over inclusion of warning language in a drug's labeling.

Manufacturers, by contrast, are in an optimal position to learn about emerging safety concerns after FDA approval, because they closely monitor the use of their products, organize postmarketing studies, and receive spontaneous reports from physicians and other sources about adverse events arising in the course of therapy (see Chapter 7). Manufacturers have a strong financial incentive to increase sales of their products, but manufacturers may also sometimes be faced with their own safety-related data that suggest limiting use of their product, or withdrawing it from the market altogether. In such situations, manufacturers have made poor decisions that adversely affect public health. For example, when drug safety issues have emerged after approval, some manufacturers have decided to downplay reports of side effects to physicians [57] and the FDA [58,59]. Failure-to-warn litigation, therefore, serves an important supplementary regulatory function – without undermining FDA requirements – by providing a disincentive (in the form of substantial monetary penalties) for manufacturers' decisions to hide or downplay reports of safety issues that emerge after a product reaches the market. Notably, former FDA commissioners have confirmed that "Although the FDA might later disapprove of a [strengthened warning] label …, the FDA's power to disapprove does not make the manufacturer's voluntarily strengthened label a violation of federal law" [60]. At any time, a manufacturer can strengthen the labeling by adding warnings to it without first notifying the FDA and receiving approval to do so. In fact, the Code of Federal Regulations states, "The labeling shall be revised to include a warning as

soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved" [61].

Despite these considerations, the FDA's amicus brief argument was repeated in subsequent failure-to-warn cases, and a few courts expressly adopted the position [62]. In 2006, the FDA attempted to solidify its position further in a surprise preamble to a set of regulations regarding the format of the label, in which it reiterated its new contention that any FDA-approved labeling, "whether it be in the old or new format, preempts … decisions of a court of law for purposes of product liability litigation" [63]. The FDA suggested that preemption should apply even if a manufacturer failed to warn adequately about a known risk, unless a patient could prove that the company intentionally committed fraud on the FDA, which is a very difficult legal standard to meet [64].

Ultimately, the US Supreme Court reviewed the legal foundation of the claimed FDA preemption of product liability related to prescription drugs. The pivotal case, *Wyeth v. Levine*, was based on a lawsuit from a patient who was treated with an intravenous antinausea medication for her migraine headache. The product extravasated and caused gangrene in her forearm, leading to amputation. The patient sued the drug manufacturer for inadequately warning on the label about the known risks of certain intravenous uses of its medication. A Vermont jury determined after fully considering the record that the label did not sufficiently describe the drug's known risks with intravenous drip administration. The manufacturer appealed the verdict, and the Vermont Supreme Court affirmed, finding that the jury's verdict did not conflict with the FDA's labeling requirements, which "create a floor, not a ceiling, for state regulation" [65].

The manufacturer appealed again to the Supreme Court, arguing that it was impossible to comply with the federally approved label and that the state court judgment would obstruct the purpose of federal drug laws. The manufacturer charged that the FDA, not the drug manufacturer, had the primary responsibility for the drug label. In a 6–3 decision, the Supreme Court upheld the Vermont decision and struck down the notion of federal preemption in this field [66]. Justice John Paul Stevens, writing for the majority, noted, "It has remained a central premise of drug regulation that the manufacturer bears responsibility for the content of its label at all times."

After *Wyeth v. Levine*, there remains no controversy about whether FDA approval of a drug label preempts failure-to-warn claims. However, the decision did leave open the possibility that preemption could be invoked if the FDA had "consider[ed] and reject[ed] a stronger warning." That is, if the FDA reviews all the data surrounding a particular safety issue and makes a specific statement that a strong warning is not necessary, such an action could be invoked by a defendant to support preemption of a failure-to-warn lawsuit.

Product Liability Law in Europe

The European Union (EU) is a political and economic coalition that currently consists of 28 countries in Europe. The main sources of EU law are regulations, directives, and decisions. Regulations are immediately enforceable in member states when they come into force and automatically override conflicting local provisions. By contrast, directives usually leave member states discretion as to how they are to be adopted [67].

Product liability has been called an "American invention" [68], and the general product liability directive for the EU (85/374/EEC) was originally enacted in 1985. A liability action arising under this directive includes the following contentions: (i) defective product; (ii) causation of damage' and (iii) no exclusion of liability.

A product is defective if it does not provide the safety that a person is entitled to expect, taking all circumstances in account, including the presentation of the product, the use reasonably expected of the product, and the time when the product was put into circulation. However, a product may not be considered defective simply because a better product was subsequently put into circulation [69].

Product liability in non-EU European countries is defined by country-specific laws, although the approach is similar to that in the EU. In Switzerland (a non-EU country), for example, there is no specific legislation covering drug liability. Nonetheless, the generally applicable Product Liability Act requires a showing of (i) damage (design defect or failure to warn); (ii) causation of damage; and (iii) no exclusion of liability.

Like in the US, most product liability lawsuits in EU and non-EU countries in Europe are based on failure-to-warn claims about the adverse event at issue, rather than design defects. One of the exclusions of liability, as in US, is the learned intermediary defense. For example, in Switzerland, a 16-year-old patient was prescribed the oral contraceptive medication drospirenone/ethinylestradiol (Yasmin) and experienced a thromboembolism with a subsequent stroke. The patient sued the manufacturer based on a failure-to-warn claim. The labelling states that there is a higher risk for thrombosis and in the information letter to the physician, the risk for a thromboembolism is reported to double with the intake of the contraceptive medication. The Supreme Court ruled that this information was sufficient [70]. As previously discussed, since DTCA is not available in Europe, it is not possible for that practice to undermine the learned intermediary defense.

Within the EU, because the product liability rule is a directive, member states retain some flexibility in implementing aspects of it, such as whether they permit compensation for noneconomic damages (e.g., pain and suffering) or which manufacturer defenses they seek to incorporate [71]. As a result of this flexibility, there is substantial diversity across EU countries in how product liability cases are adjudicated [72]. Still, countries can be limited by the directive. For example, in a series of cases, the European Court of Justice prevented France, Spain, and Denmark from enacting provisions considered to be too friendly to the damaged party [73].

Product liability related to prescription drugs in Germany bears special attention, since this is the only EU country that has implemented (even prior to the enactment of the EU liability directive) particular rules in this field via its Medicines Act. This is the consequence of the international thalidomide birth defect public health crisis of the late 1950s and early 1960s, which affected approximately 7000 children in Germany alone [74]. Liability exists if, when used in accordance with the intended purpose, the drug has harmful effects which exceed the limits considered tolerable in the light of current medical knowledge (i.e., a design defect), or the damage has occurred as a result of labelling that does not comply with current medical knowledge (i.e., a failure to warn) [75]. However, determining liability is based on a strict liability model that requires only demonstration of (i) damages; (ii) causation of damages; and (iii) no exclusions from liability (e.g., the learned intermediary defense) [76]. Another characteristic of German drug liability is the limitation of the amount of compensation for damages. In a case of death of or injury to a person, the pharmaceutical company is liable only for a capital amount of up to €600 000 or an annuity of up to €36 000 per year. In a case of death of or injury to several persons by the same drug, the pharmaceutical company shall be liable for a capital amount of up to €120 million or an annuity of up to €7.2 million per year [77].

German law also provides an interesting case example about the labeling requirements covering prescription drugs in Europe. The European Medical Agency (EMA) regularly

issues guidelines that specify the content and presentation of the labeling [78], including for example categorizing the frequency of possible side effects as very often (>10%), often (1–10%), occasional (0.1–1%), rare (0.01–0.1%), and very rare (<0.01%). In addition, Section 10 of the German Medicines Act lists all categories of information that need to be placed on a drug's labeling, such as indications, dosage, duration of intake, reference to overdose, expiration date, and adverse events. In describing adverse events, manufacturers must include a description of all adverse reactions that can occur when the drug is used as intended, the countermeasures to be taken if possible in the event of adverse reactions, and an additional standard text that explicitly instructs patients to inform their physicians, pharmacists, health professionals, or the competent higher federal authority directly of every suspected adverse reaction [79]. The German Supreme Court has ruled that more detailed information must be provided as the severity and probability of a potential adverse event increase [80].

Overall, product liability law in Europe is in many ways similar to that in the US, especially with regard to the principles of strict liability and the learned intermediary defense. However, failure-to-warn claims are less likely to succeed in Europe than in the US, and damages practices and rules generally lead to lower compensation for patients. As a result, fewer drug liability claims are brought in Europe, and the outcome of a case can vary widely whether a claim is being brought to court in the US or in a European country.

Pharmacoepidemiology and Contract Law

Many studies in the field of pharmacoepidemiology emerge from collaborations among individuals at different institutions. Different researchers may bring specific types of expertise to a project or different resources [81,82]. For example, researchers may have all the computing power they need, but require access to a certain external database to address a question. Collaborations may occur among academic centers, between nonprofit and for-profit companies, or with the government. Cooperative work can allow more complex research to be performed and help advance the field of pharmacoepidemiology in several ways.

One type of collaborative work of particular public health importance is contract research. Contract research is undertaken by an individual, academic, or nonprofit investigator supported by a sponsor (usually an industry or governmental agency). Most contractual research relationships are defined by the generation of a "deliverable," which can be a database, a research report, or some other product. The contract is the centerpiece of the relationship and classically represents the full outline of the agreement between the parties. The mutually agreed-upon terms are used as evidence of the parties' intentions if the agreement later runs into trouble and ends up in court. Relationships with industry are common; one survey of clinical epidemiologists and health services researchers in the US found that about 40% reported currently being involved in such relationships, while 50% reported forming collaborations with industry leading to publications [83]. In countless cases, contract research in pharmacoepidemiology has led to important public health findings and changes in healthcare delivery.

However, contract research may pose various potential pitfalls as well. Concern about contract research generally centers around (i) trial design; (ii) access to data and data analysis; and (iii) publication of results. It has long been known that there is a statistically significant relationship between a favorable study result and the source of research funding [84,85]. These results can be explained by choices made in trial design, when subjective decisions about

comparators [86] or the inclusion or exclusion of certain variables or potential confounders in epidemiologic and economic studies can affect the ultimate results of the trial [87]. Investigators should be wary of performing contract research in which the sponsor has the right to unduly influence the design of the trial. Many sponsors prefer to retain control of the data and insert their own statistical analyses. They argue that such efforts guard against "investigators [who] want to take the data beyond where the data should go," while investigators argue that this arrangement provides the company with an opportunity to "provide the spin on the data that favors them" [88]. In one case of an experimental AIDS vaccine, after a negative trial, the sponsor demanded that its contradictory analyses be inserted into the manuscript and ultimately sued the investigators for $7 million after the article was published [89].

Access to clinical trial data is critically important for academic researchers. In the case of rosiglitazone, a clinical trial organized by the manufacturer sought to compare the product against other treatment options for diabetes, and an independent academic steering committee was organized to oversee the data analysis [90]. Company documents suggest that the clinical trial database was exclusively controlled by the company, which provided limited access to the investigators [91]. When members of the steering committee questioned the presentation of the results, their concerns were largely overlooked [77]. In reviewing this case, one commentator concluded that the absence of independent access to all of the data in the trial may allow physician-scientists to be manipulated by the sponsor, resulting in a manuscript that does not provide the most accurate assessment of the risks and benefits of the therapy [77]. Contracts should be carefully scrutinized for the way in which they delineate who controls access to the data.

Finally, there have been conflicts over so-called gag clauses that prevent contract investigators from publishing their results [92]. For example, when a University of Toronto physician identified safety issues related to an experimental drug used to treat iron overload in transfusion-dependent patients with thalassemia [93], she was not granted permission to publish her results. When she ultimately exposed her findings, she was the subject of a breach of contract lawsuit from the sponsor, on the basis that her research contract provided that the published work-product was "secret and confidential" and could not be disclosed except with the manufacturer's "prior written consent" [94]. In the case of the cholesterol-lowering drug ezetimibe (Zetia®), the outside investigator leading a large-scale clinical trial found that the drug lacked important efficacy in cardiovascular outcomes. He reportedly pressured the manufacturer to no avail to speed the release of the data, and due to contractual obligations was unable to come forward with the data on his own without such approval [95].

Such problems are not limited to private industry contracts. In the US, a report from the Association of American Universities and the Council on Government Relations found that federal agencies commonly include controls on the dissemination of research results in their sponsored contracts and grants [96]. Contracting issues related to liability, trial design, access to data and data analysis, and publication of results are also not limited to a particular country [97]. In Europe, for example, countries aware of the challenges in setting up contracts between investigators and industry in particular offer government assistance and templates to help balance the diverging interests. In Switzerland, the ethics committee provides templates for clinical trial agreements on its website [98], and the UK and the European Commission also offer such templates and guidance notes [99].

For researchers based in academic medical centers, institutional research administration offices usually handle the details of contract

negotiation with research sponsors. However, a survey of academic medical centers in 2001 found that academic institutions routinely engage in industry-sponsored research without sufficient protection for investigators [100]. For example, a median of 1% of research administration offices (interquartile range 0–21%) in US universities reported requiring that authors have access to all the data for multicenter trials. A 2005 survey found little change. Nearly half of academic institutions reported that they allowed contract provisions permitting the research sponsor to insert its own statistical analyses and draft the manuscript, while prohibiting investigators from sharing data with third parties after a trial had ended. The survey also found that 17% of academic research centers reported disputes between researchers and sponsors about control of or access to data [101].

A few expert bodies have offered recommendations on legal guidelines for the conduct of contract research [102]. The best known and most authoritative have emerged from the International Committee for Medical Journal Editors (ICMJE). Their guidelines for original research articles submitted to biomedical journals require that the investigators be independent of the sponsors' role in the research, fully accountable for the design and conduct of the trial, have independent access to all trial data, and control all editorial and publication decisions [103]. Each of these criteria must be worked out at the beginning of the contractual relationship between the sponsor and investigators.

Whether or not they receive support from research administration offices, pharmacoepidemiologists must be aware of the ICMJE guidelines and thoroughly evaluate contracts guiding research for inappropriate language regarding control of design of the trial, access to data, and reporting of results (see Table 9.2). They should also be aware that some peer-reviewed journals have even more strict standards than the ICMJE; for example, *Pharmacoepidemiology and Drug Safety* currently requires disclosure of any control the sponsor had on the study and manuscript. Problematic language includes overly broad confidentiality clauses, clauses that define and assign ownership of intellectual property,

Table 9.2 Potentially objectionable language in research contracts for pharmacoepidemiologists.

Category	Contractual terms	Critique
Control over investigator work-product	"____ shall provide confidential information to CONSULTANT for the purpose of conducting the CONSULTANT'S professional services. All information whether written or verbal provided by, or developed for _____, and all data collected during the performance of this Agreement is deemed to be the Confidential Information of _____."	Broad definition of "confidential information" seems to cover all information. Researcher's work-product becomes sponsor's confidential information.
Gag clauses	"No information regarding this Agreement or the interest of ____ or Client in the subject matter hereof shall be disclosed to any third party without the prior written consent of _____"	Prevents disclosure of existence of the contract as a financial source in publication.
Opportunity to influence outcome	Client "shall not present or publish, nor submit for publication, any work resulting from the Services without _____ prior written approval."	Contract allows sponsor to quash publication unless it approves analyses.

All examples are anonymized but otherwise unchanged excerpts from actual contracts written to cover sponsored pharmacoepidemiologic research.

and clauses that require approval from a sponsor prior to publication. It may be reasonable to allow sponsors a limited amount of time to review proposed publications for inadvertent release of proprietary company information or to contribute suggestions based on their expertise. However, researchers have an ethical obligation to ensure that contracts do not unreasonably delay the publication of potentially important results. Poorly written contracts can lead to inappropriate secrecy of results, which can have public health concerns, as well as resulting in litigation against researchers. Balancing the contractual tightrope might not be easy, but it is important. As Dr. Curt Furberg has said, "Companies can play hardball, and many investigators can't play hardball back. You send the paper to the company for comments, and that's the danger. Can you handle the changes the company wants? Will you give in a little, a little more, then capitulate? It's tricky for those who need money for more studies" [104].

Pharmacoepidemiology and Intellectual Property Law

Patent law is a field of growing importance to the practice of pharmacoepidemiology. A patent is a formal grant of market exclusivity authorized by the federal government. The concept of a patent may have originated in ancient Greece, but became a formal legal instrument in England and Europe in the fourteenth and fifteenth centuries. In the US, the original Patent Act was passed under authority from the Constitution, which permits Congress to develop laws that "promote progress of Science and the Useful Arts" [105]. Patents give inventors the right to exclude others from making, using, offering to sell, or selling the invention claimed in the patent for 20 years from the patent application date [106]. The goal of a patent is to encourage inventors to invest in the development of their ideas, because it gives them a competition-free period in which to market a successful invention. Patents can be issued for any process, machine, manufacture, or composition of matter. To be worthy of a patent, an innovation in one of these categories must be useful, novel, and nonobvious to a person of ordinary skill in the field. These criteria aim to ensure that patents cannot be awarded for inventions that already exist, or small, noninnovative improvements on those inventions. In recent years, numerous patents have been obtained on methods and techniques used in pharmacoepidemiology, including investigating characteristics of drug use and adverse events.

In filing for a patent, an inventor must fully disclose the content of the claimed invention in a patent document. This disclosure must provide clear detail about the invention and must enable any person skilled in the art to use it, including the "best mode" (if they have contemplated one) available for making the inventions work. The process for obtaining a patent involves submitting the patent document to examiners at institutions such as the European Patent Office (EPO) and the United States Patent and Trademark Office (USPTO) who have expertise in the general subject matter of the patent. An examiner checks the application for technical accuracy and evaluates the innovativeness of the claimed invention by comparing it to previous publications and issued patents (in legal terminology, publicly available documents such as these are termed the "prior art"), to see if all the basic criteria are met. This process generally involves substantial back-and-forth between the examiner and the applicant, and may take several years to complete. Inventors may submit patent applications themselves, or enlist the help of specially trained patent agents or patent attorneys.

Inventors may have numerous justifications for pursuing patents. First, patents provide an incentive for investment in research by offering an opportunity to recoup start-up costs after

dissemination of a product. Other inventors may seek a way to publish their innovative processes while still retaining control over what they consider to be their intellectual property. A patent is classically thought of as a "quid pro quo" between inventors and society [107]. The government provides its police power to protect an inventor's intellectual property for a set length of time and, in exchange, the inventor makes the invention available to the public and fully describes it, so that others can use it and potentially improve on it in subsequent innovation. However, patents can also be controversial. Patents over scientific research tools have been implicated in barriers to effective cooperation [108], enhanced secrecy among researchers [109], and restrictions on availability of the products of research to patients [110].

Patents have become increasingly visible in the practice of pharmacoepidemiology. Most fall into the "process" category, such as methods of analyzing claims data and comparing outcomes to identify adverse events. The US Supreme Court has held that patentable processes may not include fundamental principles such as "laws of nature, natural phenomena, or abstract ideas" [111], or purely mental processes [112]. However, applications of laws of nature to a particular process may still be patentable. For example, a well-known case involved a patent over a method of curing synthetic rubber that used the Arrhenius equation to calculate the optimal cure time. The process was found to be patentable because the formula was a part of a larger inventive process for curing rubber [94].

Patents related to the practice of pharmacoepidemiology have been obtained by applicants ranging from individuals (e.g., a patent covering a method for assessing the association of genomic data with drug safety adverse event data [113]) to large healthcare data collectors such as Microsoft (e.g., a patent covering a method for large-scale data collection and data mining to infer health-related observations [114]). For example, one patent was awarded to inventors and assigned to a start-up company for a "method, system, and software for analyzing pharmacovigilance data." The patent covers a process of:

> [D]etermining a sample size-independent measure of association between two conditions of interest in the dataset of pharmacovigilance data; using a hypergeometric distribution to determine a measure of statistical unexpectedness between the conditions of interest in said dataset … and displaying the measure of association with the measure of the statistical unexpectedness to identify a significant association between conditions of interest. [115]

The concept of "hypergeometric distribution" may not be patentable as an abstract idea, but in this case the USPTO clearly considered the process patentable overall despite its integral use of that principle.

There are important ethical and legal concerns related to patenting processes that provide exclusive control over various aspects of the conduct of pharmacoepidemiology and pharmacovigilance research. First, patents that are sufficiently broad could prevent others from conducting necessary research into drug outcomes and effects, unless potentially expensive third-party licenses were negotiated beforehand. In one case, an HIV researcher at Stanford faced a patent-infringement lawsuit over a publicly available database he created to help guide antiretroviral therapy based on the resistance characteristics of the disease, because searching this database may involve a similar process to one previously patented (but never implemented) by a for-profit company [116]. In another case, a patent-seeker in the field argued that researchers should patent the adverse reactions discovered in pharmacoepidemiologic studies to enhance funding from for-profit pharmaceutical companies that might be interested in novel and nonobvious processes that link drugs and adverse events [117]. However, a

proliferation of patents over processes linking drug delivery to reported adverse events could increase costs through "another layer of bureaucrats and patent attorneys" and hurt the public health, as "real information could get easily lost in a blizzard of patented factoids" [118].

The US Supreme Court has stepped into the controversy over process patents. In 2008, the Court of Appeals for the Federal Circuit, the highest US patent appeals court below the Supreme Court, revisited its interpretation of what may be considered a patentable process. The case involved a patent over a business method for reducing risk in situations of fluctuating prices. The Federal Circuit Court held that for a process to be patentable, it must be tied to a particular machine or apparatus, or transform an object into a different state or thing [119]. Notably, as pertaining to pharmacoepidemiologic patents, the Federal Circuit Court held that "in most cases, gathering data would not constitute a transformation" because "every algorithm inherently requires the gathering of data inputs" [120]. The Supreme Court in *Bilski v. Kappos* reviewed this standard and agreed that the machine-or-transformation test was one valid way of determining whether a business method was patentable, although it was not the exclusive test [121].

Despite the Supreme Court's reluctance to draw a bright line separating patentable from nonpatentable processes, the Court's support for the machine-or-transformation test may undercut certain patents related to pharmacoepidemiology and pharmacovigilance [122]. For example, the Federal Circuit Court used the test to invalidate a patent related to a method of adverse effect detection [123]. In that case, an inventor had secured a patent on a method of using adverse event data regarding vaccine administration to inform subsequent healthcare delivery. The patent at issue claimed:

> A method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group of mammals, which comprises immunizing mammals in the treatment group of mammals with one or more doses of one or more immunogens, according to said immunization schedule, and comparing the incidence, prevalence, frequency, or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group. [124]

Pharmacoepidemiologists are likely to continue to come across patented methods in their daily work and be faced themselves with the question of whether to pursue patents on their research tools. This is particularly true in the US, where the *Bilski* decision left the door open for patents to be issued on processes involved in medical practice or pharmacoepidemiologic research.

Intellectual Property Law in Europe

In Europe, the European Patent Convention (EPC) provides the legal framework under which patents are granted. The establishment of patentability is framed in terms of fulfilling three prerequisites: novelty, usefulness, and an inventive step (equivalent to the "nonobviousness" requirement under US law) [125]. Like in the US, the maximum term of a European patent is 20 years from its filing date [126].

The US and European standards with regard to the patentability for methods and techniques are also close. The EPC provides a nonexhaustive list of nonpatentable inventions: discoveries, scientific theories, and mathematical methods; aesthetic creations; schemes, rules, and methods for performing mental acts, playing games, or doing business, and programs for computers; and presentations of information

[127]. Patents can be obtained on software according to the Technical Boards of Appeal of the EPO if the software produces a further technical effect when it runs on a computer

> which goes beyond the "normal" physical interactions between program (software) and computer (hardware). … Although it may be said that all computer programming involves technical considerations since it is concerned with defining a method which can be carried out by a machine, that in itself is not enough to demonstrate that the program which results from the programming has technical character; the programmer must have had technical considerations beyond "merely" finding a computer algorithm to carry out some procedure. [128]

According to the Guidelines for Examination in EPO, such a further technical effect can be found, for example, in the control of an industrial process or in the internal functioning of the computer itself or its interfaces under the influence of the program, or can affect the efficiency or security of a process. Software that implements a mathematical method that itself makes a technical contribution can also qualify as a further technical effect [129].

There are three possible routes for obtaining patent protection in Europe. One can apply for a patent directly to the national patent office of a particular country (national patent); one can apply for a patent to the EPO and designate specific EU member states where patent protection is wanted ("classical" European patent); or – as part of a new pathway intended to start in 2019 – one can apply for a patent to the EPO with the designation of a unitary patent that will be applicable for all of the EU member states where the government has ratified the Agreement on a Unified Patent Court [130].

The European patent system enables a central examination by the EPO, which is more efficient than the national patent process. However, granted European patents have to be subsequently validated individually in each country in which they are intended to take effect, and validation requirements can differ. The goal of the new unitary patent system is to reduce complexity and lower costs. Unitary patents will confer uniform protection, since the substantive patent law has been harmonized in the Agreement on a Unified Patent Court [131], which 25 EU member states have ratified (up to 2017) [132]. The member states also set up a Unified Patent Court to deal with the infringement and validity of unitary patents and European patents, intended to enhance legal certainty through harmonized case law in the area of patent infringement and validity and enable more efficient judicial procedures [133].

The choice among seeking a national patent, European patent, or unitary patent needs to be made depending on the preferences of the individual applicant. For example, applicants should weigh the need for broad geographic coverage versus protection in one (or a few) member states. Furthermore, consideration should also be given to whether the patent should be subject to the exclusive jurisdiction of the Unitary Patent Court, or if it is preferred to use national courts with a more limited geographic jurisdiction. While a classical European patent contains the costs for validation and renewal fees in each member state in which protection is required, the unitary patent does not include validation costs, except the cost for one translation during the transitional period as well as a single renewal fee [134].

Conclusion

Legal issues intersect with the practice of pharmacoepidemiology in many ways. Pharmacoepidemiologists may be involved in product liability cases brought by individuals against drug manufacturers, either as expert witnesses or on the basis of academic work they

undertake. These cases traditionally involve a claim of a failure to warn, which requires proof that the manufacturer knew of the safety issue, that any provided warnings were insufficient, and that the injury received was directly caused by use of the drug. Manufacturers can invoke a "learned intermediary" defense to deflect responsibility onto the treating physician, but in the US after *Wyeth v. Levine* can no longer argue that FDA approval of the drug labeling precludes providing additional warnings about adverse effects for cases in which the warnings are warranted by the data. While similar product liability rules apply in Europe, fewer cases are brought to court and damage compensation is lower.

Pharmacoepidemiologists may also be involved in contract research, but should carefully consider contractual requirements related to ownership of the work product and withholding publication.

Finally, both in the US and in Europe, pharmacoepidemiologists may decide to try to patent their research methods, but should weigh up the risks and benefits of this form of intellectual property.

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