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Drug Cos. May Find Real-World Evidence Cuts Both Ways

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(April 15, 2020, 4:03 PM EDT)

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Real-world evidence, or RWE — broadly defined by Congress as data based on the patient experience with drugs and devices from sources other than traditional clinical trials — continues to grow in popularity in the drug and device industry.

The 21st Century Cures Act, passed in 2016, provides for expanded use of RWE in the drug approval process, and companies are getting on board in exploring new opportunities. While valuable to pharmaceutical and medical device development efforts, improper use of RWE in support of mass tort litigation could lead to dubious claims that product X caused condition Y.

The growth in RWE urged by the Cures Act leads to questions of whether this wave of RWE will propel mass tort litigation, how RWE and its counterpart, real-world data, or RWD, may be used in litigation, and what practitioners can do to prepare and respond. In this article, we offer insights into these questions.

21st Century Cures Act and Real-World Evidence

In 2016, President Barack Obama signed into law the 21st Century Cures Act. One goal of the Cures Act is to accelerate drug approval, in order to keep pace with scientific developments.

In line with this goal, the Cures Act includes changes to the approval process for drug treatments, in order to speed up medical product development and innovation.[1] The Cures Act charges the U.S. Food and Drug Administration with evaluating the expanded use of RWE, including for its potential to support the approval of new indications for previously approved drugs.[2]

According to the Cures Act, RWE is data from clinical experience, meaning "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials,"[3] i.e., randomized clinical trials, or RCT. RWE is derived from analysis of RWD.

RWD can come from a range of sources, such as electronic health records, clinical data,

administrative/claims data and patient-generated/reported data. RWD can also come from digital data sources, such as health app data, wearables, other biometric devices and social media.

While the FDA has not endorsed one type of RWD over another, it has advised that RWD sources should be selected based on their suitability to address specific regulatory questions.[4] In short, RWE reflects the patient experience from individuals taking a drug or using a device in real-world settings.

Real-World Evidence in Drug and Device Regulatory Approvals

The appeal of RWE for drug and device manufacturers is readily apparent: Using RWE can accelerate drug approval and create efficiencies. In the midst of the COVID-19 pandemic, for example, RWE could aid quick regulatory approval of existing medications as treatments for COVID-19.

A flu medication, Avigan (favipiravir), has reportedly been shown to be effective in treating COVID-19 patients,[5] and pharmaceutical companies and governments are eyeing malaria drugs, chloroquine and hydroxychloroquine, as potential treatments for COVID-19.[6] Additionally, the FDA has issued an emergency use authorization to allow chloroquine and hydroxychloroquine treatment for "hospitalized teen and adult patients with COVID-19, as appropriate, when a clinical trial is not available or feasible."[7]

The FDA has announced a plan for a large clinical trial to test chloroquine for COVID-19 treatment, and remdesivir, another antiviral drug, is currently undergoing a clinical trial for the same.[8] However, there is no time to lose during a global crisis, and in addition to emergency use authorizations, quick formal approval based on RWD/RWE gathered from treatment thus far may prove valuable.

It is no surprise that since the enactment of the Cures Act, pharmaceutical companies have been ramping up their use of RWE.[9] RWD sources continue to increase through new apps, devices and software. Given that the FDA has recently issued guidance and frameworks,[10] and has used RWE to approve new indications for previously approved treatments,[11] RWE has entered the mainstream.

Use of Real-World Evidence in Mass Tort Litigation

In drug and device litigations, scientific studies are often critical in establishing and negating causation (i.e., did product X cause condition Y?). Plaintiffs point to RWE studies to show association between the alleged harm and the drug/device, often placing inappropriate weight and importance on the data when available RCT data do not support causation.

One example of experts leaning on unreliable RWE in a mass tort litigation arose in In re Avandia. In 2007 the FDA added a black box warning to Avandia, a diabetes drug, for an increased risk of heart attack.[12] In 2007, the Avandia multidistrict litigation was formed.

The Avandia MDL plaintiffs' experts heavily relied on nonrandomized observational studies.[13] Observational studies, a type of RWE,[14] are subject to confounding and bias. The district court did not exclude the plaintiffs' experts' testimony, even though the court recognized that "[n]o RCT has found a statistically significant association between Avandia and myocardial infarction."[15]

In 2013, the FDA reconsidered the 2007 Avandia label change. The FDA determined that the previous data it relied on was not statistically significant, and reviewed data from a large, long-term clinical trial. The FDA found there was in fact no increased risk between Avandia and heart attack. The FDA then

removed the black box warning regarding risk of heart attack.[16]

Given the growing popularity of RWE, parties should expect to see adversaries relying on such studies more and more. Parties need to be prepared to respond to these studies. There are many reasons defendants should be particularly skeptical of plaintiff reliance on RWE to support causation.

The gold-standard of reliability is RCTs, which, unlike nonrandomized and noncontrolled RWD collection, are designed a priori to demonstrate the safety and efficacy of a treatment intervention. RWE studies are subject to biases and confounding variables, and could yield misleading associations regarding statistically significant but noncausal outcomes. It is of critical importance that defense counsel challenge potentially unreliable RWE/RWD use in court, early and often, as causation is often an outcome-determinative factor.

Real-World Evidence and Pleadings

In recent years, plaintiffs have used RWE to propel mass tort litigation. A review of multidistrict litigation complaints reveals that plaintiffs rely on RWE studies at the inception of the mass tort litigations. Examples of this include:

- In re Farxiga (dapagliflozin) (2017): Plaintiffs cited a study based on data from an insurance claim database, to assert that defendants should have known their drug was linked to an increased risk of diabetic ketoacidosis.[17]

- In re Viagra (sildenafil citrate) and Cialis (tadalafil) (2016): Plaintiffs cited a study based on primary care data from the U.K. Clinical Practice Research Datalink to support allegations of an association between the defendants' drugs and development of melanoma.[18]

- In re Fluoroquinolone (2016): Plaintiffs relied on a study derived from adverse event reports, which had been obtained from websites formed by persons who allegedly sustained fluoroquinolone-related events, to assert that defendants should have known their drug was linked to an increased risk of peripheral neuropathy.[19]

- Testosterone Replacement Therapy (2015): Plaintiffs claimed that a paper based on data from the Veterans Affairs healthcare reporting and tracking database established the earliest date the statute of limitations could begin, asserting that prior to the paper's publication, "[p]laintiffs and their prescribing doctors did not know, and could not have known," of the risks and dangers associated with the products at issue.[20]

With the increasing use of RWE/RWD in drug and device development, defendants should prepare to combat improper use of RWE/RWD in mass tort litigation. In order to confront such potentially unreliable science as the basis for causation determinations, it is crucial to develop a strategy early.

This may include early involvement of expert witnesses who can help the defense team evaluate available clinical and real-world data. It also may include planning an early science day to educate the court about the underlying studies and data that will shape the case.[21]

Finally, it will be essential to understand the company's use of relevant RWD/RWE and its statements regarding its limitations and strengths.

Real-World Data and Plaintiff-Side Discovery

RWD can, in some circumstances, aid a manufacturer's defense. RWD offers an avenue to obtain health data regarding plaintiffs beyond just medical records.

Health tracking sources including social media, wearable devices, smartphones and other types of fitness trackers may offer insight about a plaintiff's health condition. For example, health and exercise data could show a plaintiff is not as severely injured as she claims.

Practitioners should consider preservation requests to plaintiffs, related plaintiff fact sheet requests and discovery requests to obtain such health tracking data, where appropriate. Accessing this health tracking data may require third-party subpoenas if an app or other company is storing the data.[22]

Admissibility of Real-World Evidence and Real-World Data in Federal Courts

Further along in the litigation, defendants should tailor expert discovery to probe the methodologies used by plaintiffs' experts to evaluate RWE/RWD, with the ultimate goal of bringing Daubert challenges to expert causation opinions based on RWE and RWD.

Case law addressing such challenges unfortunately is a mixed bag. While courts have recognized that RCTs are the "gold standard" for determining the relationship between a drug and a health outcome,[23] courts have found that expert opinions may still be reliable when based on RWE studies rather than RCTs. [24]

One type of RWD often addressed in litigation is adverse event reports, or AERs. Courts' analyses regarding AERs could shed light on how they will deal with other types of RWD/RWE. Despite FDA regulations advising that AERs do not constitute an admission of causation,[25] some courts have found that causation opinions based on FDA AERs are admissible, and have also admitted AERs into evidence.

A significant number of appeals courts that have addressed the issue, however, have held expert opinions based on AERs and other case reports should be excluded. As the U.S. Court of Appeals for the Tenth Circuit reasoned, AERs "contain only limited information" and are "unreliable evidence of causation."[26]

And the U.S. Court of Appeals for the Eleventh Circuit, affirming exclusion of expert testimony, reasoned that "[c]ase studies and clinical experience, used alone and not merely to bolster other evidence, are also insufficient to show general causation."[27] Likewise, numerous district courts have held that expert causation opinions based on AERs are not reliable and warrant exclusion.[28]

In addition to exclusion of expert opinions as unreliable, many courts, receptive to relevance objections, have taken the approach that adverse event information is not valid proof of medical causation, and therefore has little relevance in a product liability case.[29] Adverse event information can also be subject to challenge under Federal Rule of Evidence 403, because AERs are required to be submitted regardless of evidence of causal connection, and therefore may confuse the jury.[30]

Adverse event information is also subject to challenge as hearsay.[31] For example, the U.S. Court of Appeals for the Ninth Circuit held that a "district court did not err in excluding the adverse event reports. They were hearsay reports of uncertain reliability, lacking information relevant to causation."[32]

Conclusion

With the expansion of industry and regulatory use of RWE and RWD following enactment of the 21st Century Cures Act, we should expect to see its increased use in litigation. RWE can benefit drug and device development and public health, and RWD may offer helpful insights into individual plaintiffs' medical conditions.

However, companies should consider how RWE might be used against them in litigation, and practitioners must be prepared to address RWE from the very start of a mass tort litigation.

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[1] Framework for FDA's Real-World Evidence Program, U.S. Food & Drug Administration (Dec. 2018), at 3, https://www.fda.gov/media/120060/download.

[2] Id.

[3] 21 U.S.C. 355g(b).

[4] Framework for FDA's Real-World Evidence Program, supra, note 1 at 14.

[5] Japanese flu drug 'clearly effective' in treating coronavirus, says China, The Guardian (March 18, 2020), https://www.theguardian.com/world/2020/mar/18/japanese-flu-drug-clearly-effective-in-treating-coronavirus-says-china.

[6] See, e.g., Press Release: HHS accepts donations of medicine to Strategic National Stockpile as possible treatments for COVID-19 patients, U.S. Dep't of Health & Human Services (March 29, 2020), https://www.hhs.gov/about/news/2020/03/29/hhs-accepts-donations-of-medicine-to-strategic-national-stockpile-as-possible-treatments-for-covid-19-patients.html.

[7] See Press Release, supra, note 6; see also Emergency Use Authorization, FDA, https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization.

[8] FDA testing coronavirus treatments, including chloroquine, plasma from recovered COVID-19 patients, Tech Crunch (March 19, 2020), https://techcrunch.com/2020/03/19/fda-testing-coronavirus-treatments-including-chloroquine-plasma-from-recovered-covid-19-patients/.

[9] See, e.g., Sanofi Press Release: Sanofi and Aetion launch enterprise-wide collaboration to advance regulatory submissions using real-world evidence (Nov. 20, 2019), http://www.news.sanofi.us/2019-11-20-Sanofi-and-Aetion-launch-enterprise-wide-collaboration-to-advance-regulatory-submissions-using-real-world-evidence; BioPharma Dive: Pfizer wins expanded Ibrance approval using real world data (April 5, 2019), https://www.biopharmadive.com/news/pfizer-wins-expanded-ibrance-approval-using-real-

world-data/552135/.

[10] Framework for FDA's Real-World Evidence Program, supra, note 1; Use of Electronic Health Record Data in Clinical Investigations, Guidance for Industry, FDA (July 2018), https://www.fda.gov/media/97567/download; Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry, Draft Guidance, FDA (May 2019), https://www.fda.gov/media/124795/download; National Evaluation System for health Technology Coordinating Center (NESTcc) Methods Framework (Feb. 2020); National Evaluation System for health Technology Coordinating Center (NESTcc) Data Quality Framework (Feb. 2020), https://mdic.org/resource-library/.

[11] See, e.g., FDA approval for Ibrance in men with breast cancer sets precedent for use of real-world evidence, Pharmaceutical Technology (May 2019), https://www.pharmaceutical-technology.com/comment/real-world-evidence-in-pharma/.

[12] Avandia Label and Medication Guide (2008), https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021071s034lbl.pdf.

[13] See In re Avandia Mktg., Sales Pracs. & Prod. Liab. Litig., No. 2007-MD-1871, 2011 WL 13576 (E.D. Pa. Jan. 4, 2011).

[14] Framework for FDA's Real-World Evidence Program, supra, note 1 at 5-6.

[15] In re Avandia Mktg., 2011 WL 13576, at *2, n.10.

[16] FDA Drug Safety Communication: FDA requires removal of some prescribing and dispensing restrictions for rosiglitazone-containing diabetes medicines (Nov. 25, 2013), http://www.fda.gov/Drugs/DrugSafety/ucm376389.htm.

[17] In re Farxiga (Dapagliflozin) Prods. Liab. Litig., 17-MD-2776 (LGS) (S.D.N.Y. Sept. 6, 2017) Amended Master Long-Form Complaint, Dkt. 79-2, ¶ 141; Fralick, et al., Risk of Diabetic Ketoacidosis after Initiation of an SGLT2 Inhibitor, 376 N. Engl. J. Med. 2300 (June 2017), https://www.ncbi.nlm.nih.gov/pubmed/28591538.

[18] In re Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Prods. Liab. Litig., 3:16-md-02691-RS (N.D. Cal. Sept. 9, 2016) Master Long Form Complaint, Dkt. 98, ¶ 36, n. 17; Matthews et al., Phosphodiesterase Type 5 Inhibitors and Risk of Malignant Melanoma: Matched Cohort Study Using Primary Care Data from the UK Clinical Practice Research Datalink, PLOS Med. (June 14, 2016), https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002037.

[19] In re Fluoroquinolone Prods. Liab. Litig., 0:15-md-02642-JRT (D. Minn. April 28, 2016) Master Complaint, Dkt. 162, ¶ 79; Cohen, JS, Peripheral Neuropathy Associated with Fluoroquinolones (Dec. 2001), https://www.ncbi.nlm.nih.gov/pubmed/11793615.

[20] Testosterone Replacement Therapy Prods. Liab. Litig., 1:14-cv-01748 (N.D. Ill. Nov. 24, 2015) Third Amended Master Long-Form Complaint, Dkt. 1074, ¶¶ 411, 415; Vigen et al., Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels, JAMA (Nov. 6, 2013), https://jamanetwork.com/journals/jama/fullarticle/1764051.

[21] For more information on planning a science day from the authors of this article, see Passaretti-Wu, R., et al., Science Days in Mass Torts, DRI, In-House Defense Quarterly (Summer 2019).

[22] See ABA Practice Points: "Steps" for Discovery: Subpoenaing Wearable Technology Data (May 14, 2019), https://www.americanbar.org/groups/litigation/committees/products-liability/practice/2019/steps-for-discovery-subpoenaing-wearable-technology-data/.

[23] See, e.g., In re Rezulin Prod. Liab. Litig., 369 F. Supp. 2d 398, 406 (S.D.N.Y. 2005).

[24] Compare In re Abilify (Aripiprazole) Prods. Liab. Litig., 299 F. Supp. 3d 1291 (N.D. Fla. 2018) (permitting expert to rely on non-RCT evidence to support causation); In re Fosamax Prods. Liab. Litig., 645 F. Supp. 2d 164 (S.D.N.Y. 2009) (same); with Kilpatrick v. Breg Inc., 613 F.3d 1329 (11th Cir. 2010) (prohibiting expert from relying on study derived from medical records to establish causation); In re Accutane Prod. Liab., 511 F. Supp. 2d 1288, 1298 (M.D. Fla. 2007) (prohibiting expert from relying on case reports to establish causation).

[25] 21 CFR § 314.80(k)(1).

[26] Hollander v. Sandoz Pharms. Corp., 289 F.3d 1193, 1211 (10th Cir. 2002).

[27] Hendrix v. Evenflo Co., 609 F.3d 1183, 1197 (11th Cir. 2010).

[28] See, e.g., In re Zicam Cold Remedy Mktg., Sales Pracs., & Prods. Liab. Litig., 2011 WL 798898, at *11 (D. Ariz. Feb. 24, 2011); Rhodes v. Bayer Healthcare Pharms. Inc., 2013 WL 1289050, at *5-6 (W.D. La. Mar. 26, 2013); DeGidio v. Centocor Ortho Biotech Inc., 3 F. Supp. 3d 674, 684-86 (N.D. Ohio Mar. 11, 2014); In re Mirena Ius Levonorgestrel-Related Prods. Liab. Litig. (No. II), 341 F. Supp. 3d 213, 267-68 (S.D.N.Y. Oct. 24, 2018).

[29] See, e.g., Smith v. Pfizer Inc., 2010 WL 1754443, at *6 (M.D. Tenn. April 30, 2010).

[30] In re Norplant Contraceptive Prods. Liab. Litig., MDL No. 1038, 1997 WL 80527, at *1 (E.D. Tex. Feb. 19, 1997).

[31] Klein v. TAP Pharm. Prods. Inc., 518 F. App'x 583 (9th Cir. 2013).

[32] Id. at 584.