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Off-Label Use of Prescription Drugs

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SUMMARY

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Off-Label Use of Prescription Drugs

When the Food and Drug Administration (FDA) approves a drug for sale in the United States, the approval includes a section entitled "Indications for Use." This section lists the one or more diseases, conditions, or symptoms for which the drug's sponsor (usually the manufacturer) has provided, to FDA's satisfaction, evidence in support of the drug's safety and effectiveness. FDA approval is also based on its review of the drug's dosage, packaging, manufacturing plan, and labeling. Before changing any of those elements, the sponsor must inform, and usually receive permission from, FDA.

In essence, FDA regulates all approval and post-approval aspects of a drug product. But FDA traditionally has not regulated the practice of medicine. Physicians, therefore, may prescribe an FDA-approved drug for indications that FDA has not reviewed for safety and effectiveness. Those uses, furthermore, are not addressed in the labeling information regarding, among other things, dosing, warnings about interactions with other drugs, and possible adverse events.

How Are Off-Label Prescription Drugs Used?

Prescribing for so-called off-label uses can be accepted medical practice, often reflecting cutting-edge clinical expertise. For example, this is the case with oncology drug use, more than half of which is off-label. Off-label prescribing can be a reasonable choice when labeling overlooks certain populations—for example, when a drug tested in adults is prescribed to children. A drug may be used off-label when it was tested for the treatment of one disease and prescribed in an attempt to prevent or treat another, when it was tested at one dose and used at higher or lower doses, or when it was tested in an eight-week trial and prescribed for long-term use. Estimates for how common off-label prescriptions are in the United States are hardly precise. Credible researchers have estimated they make up as little as 12% and as much as 38% of doctor-office prescriptions.

What Are the Risks of Off-Label Prescriptions?

Prescriptions for off-label uses of FDA-approved drugs are made without the benefit of an FDA-reviewed analysis of safety and effectiveness data. Physicians may resort to such prescribing to take advantage of new ideas and treatment approaches when available information to support them is inadequate. However, despite the potential risks associated with off-label uses, efforts to prohibit such uses might hurt the public. Some off-label prescribing may result because manufacturers have chosen not to invest the resources needed to have FDA add indications to the drug's approval and labeling.

A worst-case scenario for the nation's health would be the widespread acceptance of a drug for an off-label use that sufficient research would have revealed to be ineffective, unsafe, or both. Aside from the drug's direct harm, the time spent waiting to see whether it worked would have been time not spent exploring other treatment options.

Unchecked off-label prescribing may also threaten the FDA gold standard of drug approval. If clinicians had already accepted a new use into practice through off-label prescribing, a manufacturer may choose to not invest resources to go through clinical trials and the FDA process to win approval.

Although manufacturers do share information on off-label uses, courts have sometimes found they had overstepped allowable bounds. Congress has given permission for limited sharing. Are there other ways to share clinical information that do not put the public's health or FDA's authority at risk?

What Role Can Congress Play in the Use of Off-Label Prescriptions?

How might Congress, in its legislative or oversight roles, consider the use of off-label drugs to protect the public's health? Legislators and health analysts have suggested both restrictive and permissive actions regarding off-label use. Ideas—some of which conflict with others—include

- disclosure to patients;
- data collection, availability, and analysis;
- dissemination of clinical data;
- linking reimbursement and coverage to evidence of safety and effectiveness;
- clinical research and research transparency;
- clinical guidance;
- congressional oversight through the Government Accountability Office, the Federal Trade Commission, and the Department of Health and Human Services; and
- consideration of other countries' approaches to off-label use.

Some actions would require federal legislation. Other proposals would involve actions by other entities, such as state authorities and professional organizations, which Congress could urge.

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Introduction

Both legislators and regulators have expressed concern about the safety and effectiveness of prescription drugs prescribed for "off-label uses"—purposes other than those for which the Food and Drug Administration (FDA) has approved their sale.[1] Two recent incidents illustrate the bases for those concerns.

The first involves a drug already on the market. Safety experts raised concerns about ketamine, a drug available as an injectable anesthetic.[2] They noted that physicians have created outpatient clinics to administer intravenous ketamine in an off-label use to treat depression and migraines.[3] FDA has not reviewed clinical data that could support the clinics' promotional claims of safety and effectiveness.[4]

In August 2018, a second incident occurred in a Texas courtroom. Astra Zeneca settled a case concerning its alleged promotion of Seroquel for uses other than those for which it had sought and obtained FDA approval for sale in the United States.[5] The core of the complaint by the state of Texas was that the company promoted the drug's use in children, although the FDA-approved labeling of the drug was for adult use. It was one of a number of settlements since 2000 resulting in payments by drug companies for the promotion of off-label uses.[6]

To help understand the issues involving off-label use, and how these issues might concern Congress, this report addresses five questions:

- What is drug labeling? What is off-label use?
- How are off-label prescriptions used in medicine today?
- What are the risks and benefits associated with off-label prescriptions?

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[1] FDA Memorandum, "Public Health Interests and First Amendment Considerations Related to Manufacturer Communications Regarding Unapproved Uses of Approved or Cleared Medical Products" January 2017, https://www.regulations.gov/document?D=FDA-2016-N-1149-0040. See **Table A-1** for selected history of congressional concerns.

[2] Megan Thielking, "A STAT Investigation: Ketamine gives hope to patients with severe depression. But some clinics stray from the science and hype its benefits," STAT, September 24, 2018, https://www.statnews.com/2018/09/24/ketamine-clinics-severe-depression-treatment; and Melvyn W. Zhang, Keith M. Harris, and Roger C. Ho, "Is Off-label repeat prescription of ketamine as a rapid antidepressant safe? Controversies, ethical concerns, and legal implications," BMC Medical Ethics, vol. 17, no. 4, published online January 14, 2016, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4714497/pdf/12910_2016_Article_87.pdf.

[3] See, for example, Actify Neurotherapies, https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PsychopharmacologicDrugsAdvisoryCommittee/UCM631429.pdf.

[4] In March 2019, FDA approved a new drug application for *intranasal* esketamine for treatment-resistant depression (FDA, "FDA approves new nasal spray medication for treatment-resistant depression; available only at a certified doctor's office or clinic," News Release, March 5, 2019, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm632761.htm?dom=prime&src=syn).

[5] Ken Paxton, Attorney General of Texas, "AG Paxton Recovers $110 Million for Texas in Medicaid Fraud Settlements," News Release, August 7, 2018, https://www.texasattorneygeneral.gov/news/releases/ag-paxton-recovers-110-million-texas-medicaid-fraud-settlements; https://www.texasattorneygeneral.gov/sites/default/files/files/epress/Seroquel_SA_Fully_Executed.pdf.

[6] For example, Department of Justice, "GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data," Office of Public Affairs, July 2, 2012, https://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report; and Department of Justice, "Fact Sheet: Significant False Claims Act Settlements & Judgments, Fiscal Years 2009-2016," https://www.justice.gov/opa/press-release/file/918366/download.

- What concerns, if any, does Congress have about such prescriptions?
- If Congress wanted to do something about off-label prescriptions, what would be some of the options?

Drug Labeling and Off-Label Use

To market a prescription drug in the United States, a manufacturer needs FDA approval.[7] To obtain that approval, the manufacturer must demonstrate the drug's safety and effectiveness according to criteria specified in law and agency regulations. It must also ensure that its manufacturing plant passes FDA inspection.

Finally, it must obtain FDA approval for the drug's labeling—a term that covers all written material about the drug, including, for example, packaging, prescribing information for physicians, and patient brochures. FDA, thus, approves the drug and its labeling for a specific use. That use specifies the disease or condition, the population, and the way the drug is packaged and administered.

When a physician prescribes a drug for reasons other than those specified in the FDA approval and labeling, the medical profession considers this to be *off-label use*.

FDA regulates the drug and the manufacturer. Each state regulates clinicians and pharmacies.[8] A licensed physician may—except in highly restricted circumstances[9]—prescribe the approved drug without limitation. A prescription to an individual whose demographic or medical characteristics differ from those indicated in a drug's FDA-approved labeling is accepted medical practice.

In a 2006 study of drug prescribing by office-based physicians, 21% of prescriptions were written for off-label uses. Of those off-label prescriptions, the study's authors found that 27% were backed by strong scientific support.[10] A 2016 Canadian study of primary care clinics found an overall rate of 12% of prescriptions for off-label uses. The percentage varied, however, by therapeutic class, ranging from 5% for ear, nose, and throat medications to 25% for central

[7] FDA-approved drugs are designated by law into only two categories: prescription and nonprescription (also referred to as over-the-counter). No drug was prescription-only until the 1951 Humphrey-Durham amendments [P.L. 82-215, the Food, Drug, and Cosmetics Act Amendments Act, 1951], which stated, "A drug intended for use by man which ... because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, is not safe for use except under the supervision of a practitioner licensed by law to administer such drug" (FFDCA §503(b)(1)). See CRS In Focus IF10463, *Regulation of Over-the-Counter (OTC) Drugs*.

[8] The FFDCA does not give FDA authority to regulate the practice of medicine; that responsibility generally rests with the states and medical professional associations.

[9] FDA may place restrictions on prescribing or dispensing as "elements to assure safe use" (ETASU) as part of a risk evaluation and mitigation strategy (REMS) that the agency may require (see FFDCA §505-1(f)).

[10] David C. Radley, Stan N. Finkelstein, and Randall S. Stafford, "Off-label Prescribing Among Office-Based Physicians," Archives of Internal Medicine, vol. 166, May 8, 2006. The authors note, "[a]n indication was considered to be scientifically supported if, according to DRUGDEX, its effectiveness has been shown in controlled trials or observed in clinical settings."

nervous system medications.[11] An econometric model from the National Ambulatory Medical Care Survey estimated a 38% rate of off-label use.[12]

Research has shown that more than half of oncology drug use is off-label. A 2018 study examined 43 FDA-approved cancer drugs and compared their 99 labeled uses with the acceptable uses published by a national compendium Medicare relies on to make coverage decisions.[13] Of the 451 compendium-accepted uses, 56% were off-label. Of the off-label uses, the authors deemed 91% as "well-accepted off-label use."[14]

Labeling: History, Requirements, and Value

History. Drug labeling has been central to FDA's role as a protector of the public's health since 1906. That year, Congress (1) required that sellers state on a drug's label the "quantity or proportion of any alcohol [or] opium" contained, and (2) considered as "misbranded" any drug whose label was "false or misleading." Requirements that drugs be safe were not established until 1938. Congress did not require they be effective until 1962.[15]

Requirements. Today, a drug's labeling is more than the sticker the pharmacy places on the amber vial it dispenses to a customer.[16] The Federal Food, Drug, and Cosmetics Act (FFDCA) and associated FDA regulations[17] require and describe a product's labeling as "a compilation of information about the product, approved by FDA, based on the agency's thorough analysis of the new drug application (NDA) or biologics license application (BLA) submitted by the applicant. This labeling contains information necessary for safe and effective use."

[11] Tewodros Eguale, David L. Buckeridge, Aman Verma, Nancy E. Winslade, Andrea Benedetti, James A. Hanley, Robyn Tamblyn, "Association of Off-label Drug Use and Adverse Drug Events in an Adult Population," *JAMA Internal Medicine*, vol. 176, no. 1, January 2016, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2467782.

[12] W. David Bradford, John Turner, and Jonathan W. Williams, "Off-Label Use of Pharmaceuticals: A Detection Controlled Estimation Approach," presentation at the Innovation and Behavior in Health Markets Conference, 2016, revised May 24, 2018, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2230976.

[13] Michael B. Shea, Mark Stewart, Hugo Van Dyke, Linda Ostermann, Jeff Allen, and Ellen Sigal, "Outdated Prescription Drug Labeling: How FDA-Approved Prescribing Information Lags Behind Real-World Clinical Practice," Therapeutic Innovation & Regulatory Science, vol. 52, issue 6 (first published online March 5, 2018; issue published November 1, 2018), https://www.focr.org/sites/default/files/pdf/FOCR-Labeling-Research-Article.pdf?eType=EmailBlastContent&eId=067b86ca-de59-4767-86ab-8a4ad95a7978; abstract at https://journals.sagepub.com/doi/full/10.1177/2168479018759662.

[14] The authors (Shea et al.) defined "well-accepted off-label drug use" if the National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium graded the use in its top two categories of evidence.

[15] Federal Food and Drug Act of 1906 (F&DA), P.L. 59-384, 1906; Federal Food, Drug, and Cosmetic Act (FFDCA), P.L. 75-717, 1938; and Kefauver-Harris Drug Amendments to the FFDCA, P.L. 87-781, 1962.

[16] For examples of labeling, search for a drug at Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/).

[17] FFDCA Section 201(m), 21 C.F.R. Part 201—Labeling, and FDA, "[Docket No. 2000N–1269] (formerly Docket No. 00N–1269) RIN 0910–AA94, Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," *Federal Register*, vol. 71, no. 15, January 24, 2006, pp. 3922-3997, http://www.gpo.gov/fdsys/pkg/FR-2006-01-24/pdf/06-545.pdf.

FDA requires that labeling begin with a highlights section that includes, if appropriate, black-box warnings, so called because their black borders signify importance.[18] The regulations list the required elements of labeling:[19]

• indications and usage • dosage and administration • dosage forms and strengths • contraindications • warnings and precautions • adverse reactions	• drug interactions • use in specific populations • drug abuse and dependence • overdosage • description • clinical pharmacology	• nonclinical toxicology • clinical studies • references • how supplied/storage and handling • patient counseling information

Value. Labeling plays a major role in the presentation of safety and effectiveness information. For clinicians, it is a primary source of prescribing information. The manufacturer submits the approved labeling for publication in the widely used *Physician's Desk Reference*. That labeling also serves as the basis for several patient-focused information sheets that manufacturers, pharmacy vendors, and many web-based drug information sites produce.[20]

Off-Label Use: Description and Examples

Off-label prescribing can reflect cutting-edge clinical expertise. It can also be a response to price: a physician may choose to prescribe a lower-priced drug instead of a specifically labeled higher-priced one. Or a physician may prescribe off-label in an attempt to try a different treatment approach when other options have failed.

Sometimes an off-label use becomes so widespread that it becomes accepted practice. However, without the backing of carefully designed clinical trials and expert analysis, it remains unknown whether the drug is, in fact, safe and effective for the off-label use. Also unknown are dosing details and systematically evaluated associated adverse events.

Examples of off-label use include

- a drug tested for the treatment of one disease prescribed in an attempt to prevent or treat another;
- a drug tested at one dose used at higher or lower doses;
- a drug tested in adults prescribed to children; and
- a drug tested in an eight-week trial prescribed for long-term use.

Table 1 lists several examples of FDA-approved drugs widely prescribed for off-label uses.

[18] "Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box" (21 C.F.R. 201.57(c)(1)).

[19] 21 C.F.R. 201.56(d). For older drugs, labeling content requirements are listed in 21 C.F.R. 201.56(e).

[20] PDR Network, http://www.pdr.net/about-pdr-network/. Examples of consumer medication information materials include those by Wolters Kluwer Health, Inc. (used, for example, with Target dispensing, http://www.consumerreports.org/health/best-buy-drugs/prescription-labels/patient-instructions/index.htm); First Databank, Inc. (provides FDA Medication Guides, http://www.fdbhealth.com/solutions/retail-pharmacy-dispensing/); and American Society of Health-System Pharmacists Consumer Medication Information (http://www.ahfsdruginformation.com/products_services/ahfs_cmi.aspx).

Table 1. Selected Off-Label Uses

Drug	Labeled Uses	Off-Label Uses
gabapentin	post-herpetic pain; epilepsy seizures	peripheral diabetic neuropathy; menopausal hot flashes; attention deficit disorder; bipolar disorder
ketamine	anesthesia	depression, migraines
fentanyl	"management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate"[a] "management of breakthrough pain in cancer patients … who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain"[b]	less severe or chronic pain; for individuals who are not opioid-tolerant
antipsychotics (e.g., risperidone, olanzapine, quetiapine)	schizophrenia; bipolar disorder	sleep aid; behavioral symptoms of dementia; obsessive compulsive disorder, posttraumatic stress syndrome, anxiety disorders[c]
methylphenidate	attention deficit disorders in children; narcolepsy[d]	attention deficit disorders in adults, depression, autism spectrum disorder
Avastin	certain non-squamous non-small cell lung cancer; glioblastoma, renal cell carcinoma, cervical cancer, epithelial ovarian, fallopian tube, or primary peritoneal cancer	wet age-related macular degeneration; colorectal cancer

Source: Labeled uses excerpted from FDA-approved labeling posted at Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/). Examples of off-label uses compiled by CRS based on clinical databases and news accounts.

a. Labeling for Duragesic (transdermal), a brand-name fentanyl product.

b. Labeling for Subsys (sublingual), a brand-name fentanyl product.

c. "Off-Label Use of Atypical Antipsychotics: An Update," Comparative Effectiveness Review No. 43, John M. Eisenberg Center for Clinical Decisions and Communications Science, August 1, 2012, http://www.effectivehealthcare.ahrq.gov/offlabelantipsych.cfm.

d. Labeling from Ritalin, a brand-name methylphenidate product.

Although FDA materials do not list off-label uses, several drug compendia include both labeled and off-label uses. For Medicare coverage, for example, the Social Security Act defines "medically accepted indication" as those, in addition to uses approved by FDA, that have been evaluated and supported and listed in one of several compendia, or for which there is "supportive clinical evidence in peer reviewed medical literature."[21]

[21] Social Security Act §1861(t)(2)(B) [42 U.S.C. 1395x]. Compendia—available by subscription—include the American Hospital Formulary Service's Drug Information, National Comprehensive Cancer Network Drug and Biologics Compendium, and Thomson Micromedex DrugDex.

Benefits and Risks of Off-Label Use

Why has Congress given FDA the authority to regulate whether a drug may be on the U.S. market? Two key reasons: to protect patients and to encourage research in a competitive pharmaceutical industry.[22]

By statute and regulation, FDA now approves a drug for a specific use once its sponsor (usually the manufacturer) has provided sufficient evidence that the drug is safe and effective for that use. FDA has developed procedures for the review of that evidence. The FDA-approved labeling, which informs the clinician about dosing and likely and unlikely adverse events, helps protect the individuals for whom the drug is prescribed.

Labeling also helps protect the interests of the manufacturers who invest in the clinical trials that demonstrate safety and effectiveness. For new drugs and new uses of already approved drugs, the sponsor receives a period of market protection, in the form of regulatory exclusivity for the sale of the drug for those uses. Payors—such as private health insurers or Medicare—benefit from FDA-approved labeling in their evaluation of whether to pay for a drug's use.

But use of a drug evolves as clinicians (and the manufacturer) share their experiences regarding off-label uses, which, by definition, were not part of the premarket clinical studies used to obtain FDA approval. Off-label use can benefit patients. In some instances, such as in the treatment of rare diseases, clinical practice may use drugs approved for other indications. A manufacturer may choose not to invest in trials for such a small patient group.[23] A patient whose physician is already prescribing the drug off-label may not want to enroll in a clinical trial where there is a chance he or she may be assigned to the placebo group. Once drugs are well-established in off-label uses, manufacturers rarely design studies to determine or verify the safety and effectiveness of such uses. Individuals and groups wanting to conduct such studies may find it hard to obtain funding.

Examples of adverse events (AEs) associated with the use of drugs for specific off-label uses include heart valve damage from the use of fenfluramine and phentermine (fen-phen) for weight loss, and seizures from the use of tiagabine hydrochloride for depression.[24] Using a Canadian primary care database that captured all prescriptions, the reason for each prescription, and adverse events, researchers looked at the rate of AEs for on-label use, off-label use associated with "strong scientific evidence," and off-label use without such evidence. They found more AEs for off-label prescriptions than for on-label prescriptions. However, off-label use associated with strong scientific evidence had similar rates of AEs as did on-label uses. The increased risk of AEs for off-label use was concentrated in those uses without strong scientific evidence.[25]

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[22] FDA statement at https://www.fda.gov/AboutFDA/Transparency/Basics/ucm194877.htm; and FFDCA §1003 [21 U.S.C. 393].

[23] See, for example, testimony to FDA by the National Organization for Rare Disorders, November 9, 2016, https://rarediseases.org/wp-content/uploads/2014/11/2016-11-09.-NORD-Statement-at-FDA-Off-Label-Public-Hearing.pdf.

[24] Tewodros Eguale, David L. Buckeridge, Aman Verma, Nancy E. Winslade, Andrea Benedetti, James A. Hanley, Robyn Tamblyn, "Association of Off-label Drug Use and Adverse Drug Events in an Adult Population," *JAMA Internal Medicine*, vol. 176, no. 1, January 2016, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2467782.

[25] Tewodros Eguale, David L. Buckeridge, Aman Verma, Nancy E. Winslade, Andrea Benedetti, James A. Hanley, Robyn Tamblyn, "Association of Off-label Drug Use and Adverse Drug Events in an Adult Population," *JAMA Internal Medicine*, vol. 176, no. 1, January 2016, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2467782.

Manufacturers benefit from sales for off-label uses. However, they risk losing that market should a competitor complete studies to obtain FDA approval and labeling for those uses. Researchers who are not supported by the manufacturer who try to assess the safety and effectiveness of off-label uses are hampered by the inexact nature of secondary data sources: the standard clinical trial data collection in preparation for an FDA application is not available for off-label uses. What may begin as hopeful and intermittent off-label use may gain momentum and offer opportunities for planned studies.

Drug and device companies argue that current regulations prevent them from distributing important information to physicians and payors about unapproved, off-label uses of their products.[26] In November 2016, FDA held a two-day public meeting to hear from various groups regarding off-label uses of approved or cleared medical products.[27] In June 2018, FDA issued final guidances explaining the agency's policy about medical product communications that include data and information not contained in FDA-approved labeling.[28]

One FDA guidance document, in particular, described the types of information that a manufacturer could provide payors and formulary committees about unapproved uses of approved products.[29] FDA made two points especially relevant to off-label uses.

First, FDA differentiates among its audiences in its presentation of information. The material it allows in product labeling is directed to a clinical audience. FDA staff have reviewed the information and require that it be presented in a way that is understandable by individual clinicians, who often do not have the statistical sophistication or data analysis skills or resources to fully evaluate the claims of manufacturers. This guidance notes, though, that payors and formulary committees do have such expertise and resources. FDA also acknowledges that it is useful for payors to have information in their decisions on coverage, but it wants to ensure that the information manufacturers provide is not misleading.

Second, the FDA guidance describes what harm could come from allowing more sharing of information about off-label use.

> Some firm communications regarding unapproved products or unapproved uses of approved/cleared/licensed medical products may potentially undermine substantial government interests related to health and safety. These interests include motivating the development of robust scientific data on safety and efficacy; maintaining the premarket review process for safety and efficacy of each intended use in order to prevent harm, to protect against fraud, misrepresentation, and bias, and to develop appropriate instructions for use for medical products; protecting the integrity and reliability of promotional

[26] STAT, "FDA to hold long-awaited meeting to review off-label marketing," August 31, 2016, https://www.statnews.com/pharmalot/2016/05/27/fda-hhs-free-speech-patient-safety/.

[27] FDA, Docket No. FDA-2016-N-1149, https://s3.amazonaws.com/public-inspection.federalregister.gov/2016-21062.pdf. All prescription drugs must receive FDA approval for marketing. About 1% of medical devices go through a comparable approval process; most devices receive FDA clearance for marketing. For a description of FDA medical device regulation, see CRS Report R42130, *FDA Regulation of Medical Devices*.

[28] FDA, "Guidance for Industry: Medical Product Communications That Are Consistent With the FDA-Required Labeling—Questions and Answers," Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, Center for Veterinary Medicine, and Office of the Commissioner, June 2018, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf.

[29] FDA, "Guidance for Industry and Review Staff: Drug and Device Manufacturer Communications With Payors, Formulary Committees, and Similar Entities—Questions and Answers," Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, and Office of the Commissioner, June 2018, https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537347.pdf.

information regarding medical product uses; and preventing the diversion of health care resources toward ineffective treatments.

The concerns FDA raised in the June 2018 final guidance documents might explain why Congress may be interested in exploring the issue of off-label use further.

History of Congressional Interest and Action

Congress has developed a system to protect the public by ensuring that drugs sold in the United States have met clinical and manufacturing standards of safety and effectiveness. Labeling is the mechanism that bridges the regulated drug and the use of that drug in clinical practice. The labeling establishes the uses for which the manufacturer has demonstrated safety and effectiveness to FDA's satisfaction. Congress and the FDA have tried several approaches, using labeling as a tool, to reduce the risk to patients. **Table A-1** includes examples of congressional and FDA actions to expand the information provided in a drug's labeling. The actions have addressed topics such as

- content labeling,
- directions for use,
- permissible and prohibited advertising,
- research incentives to support labeling specific to population subgroups (e.g., children),
- criteria for Medicare coverage,
- required and permissible labeling changes, and
- balance of benefit and risk information in labeling and advertising.

Manufacturers, meanwhile, want to be able to provide information to insurers and other entities (such as the Centers for Medicare and Medicaid Services [CMS] and hospital pharmacy and therapeutics committees) that decide whether to cover a drug in a policy and whether to limit reimbursement for specific uses. Congress has provided some leeway relative to its earlier prohibition on promotional activities. For example, in 2016, it broadened the types of health care economic information drug and device manufacturers could provide to payors (e.g., insurance companies).[30] Although the underlying FFDCA section continues to exclude information related only to an off-label use, it now requires "a conspicuous and prominent statement describing any material differences between the health care economic information and the labeling approved for the drug." Several bills concerning off-label use have been introduced that would have expanded the information that manufacturers could provide about off-label uses. For example, the Subcommittee on Health of the House Committee on Energy and Commerce marked up H.R. 2026 (115th Congress), the Pharmaceutical Information Exchange Act, in January 2018, which would have allowed the provision of *scientific information* to payors, in addition to health care economic information.[31] Then-Subcommittee Chair Michael Burgess, in commenting on the bill's effort to clarify how manufacturers can share "if it is based on competent and reliable evidence," expressed strong support for the bill. He noted "the importance of cutting edge information in

[30] Sec. 3037 of P.L. 114-255, the 21st Century Cures Act.

[31] Subcommittee on Health, House Committee on Energy and Commerce, mark-up of H.R. 2026, January 17, 2018, https://energycommerce.house.gov/committee-activity/markups/markup-of-hr-over-the-counter-monograph-safety-innovation-and-reform-act.

medicine and science to optimize patient care and outcomes … and [how the bill] could have the potential to save patients' lives."[32]

Then-Ranking Member (now, Chair) Frank Pallone, Jr., though, argued that the ability to communicate about off-label use "had great potential to undermine" FDA's approval process and to "hamstring" its enforcement efforts.[33] H.R. 2026 passed the subcommittee, although it did not reach the floor in the 115th Congress.

Possible Avenues of Future Congressional Interest

Off-label use presents both opportunities and risks to clinicians, patients, manufacturers, and researchers. At times, those interests clash. Academics, public health organizations, and journals have suggested what actions Congress might take based on their particular concerns regarding off-label prescriptions.[34] These actions include both direct legislation and oversight activities to encourage action by other entities. The 116th Congress might consider some of these varied approaches, summarized in the issues described below.

Disclosure to patients. Most individuals, unaware of the nuances of FDA regulation, may not know that physicians may prescribe drugs for uses that FDA has not reviewed for safety and effectiveness. Several potential opportunities for providing this information exist. Congress could require or work with the states to require that

- the prescriber inform the patient about the off-label use and describe the meaning of off-label use;
- the prescriber note in the prescription why the drug is being prescribed; or
- the pharmacist inform the patient that the use is off-label.

Data collection and availability. FDA, under federal law, determines whether a drug requires a prescription. The states, under their individual laws, determine what information the prescription order contains. Because clinicians do not need to note on the prescription order why they are prescribing a drug (e.g., simvastatin for high cholesterol or citalopram for depression), the information in pharmacy, administrative, and clinical databases often cannot directly identify off-label uses. Therefore, as Congress and other public policy groups consider whether and how to address off-label drug prescribing, they do not have adequate information on the scope and details of the practice. Congress could require or work with the states to encourage

[32] Subcommittee on Health, House Committee on Energy and Commerce, mark-up of H.R. 2026, January 17, 2018, https://energycommerce.house.gov/committee-activity/markups/markup-of-hr-over-the-counter-monograph-safety-innovation-and-reform-act.

[33] Subcommittee on Health, House Committee on Energy and Commerce, mark-up of H.R. 2026, January 17, 2018, https://energycommerce.house.gov/committee-activity/markups/markup-of-hr-over-the-counter-monograph-safety-innovation-and-reform-act.

[34] For example: Zachary Brennan, "New Report Investigates Drivers of Off-Label Prescribing in the EU," Regulatory Focus, March 3, 2017; Christine Fukada, Jillian Clare Kohler, Heather Boon, Zubin Austin, and Murray Krahn, "Prescribing gabapentin off label: Perspectives from psychiatry, pain and neurology specialists," CPJ/RPC, vol. 145, no. 6, November/December 2012; Megan Thielking, "A STAT Investigation: Ketamine gives hope to patients with severe depression. But some clinics stray from the science and hype its benefits," STAT, September 24, 2018, https://www.statnews.com/2018/09/24/ketamine-clinics-severe-depression-treatment; and Joshua D. Wallach and Joseph S. Ross, "Gabapentin Approvals, Off-Label Use, and Lessons from Postmarketing Evaluation Efforts," *JAMA*, vol. 319, no. 8, February 27, 2018.

- clinicians to note on prescriptions the reason for medication use (e.g., the specific condition, disease, or symptom), thereby allowing that information to appear in pharmacy databases, which would enable focused analysis of off-label uses;
- the establishment of confidential registries of off-label prescribing and follow-up information that FDA (or other designated scientifically appropriate agencies) could use in its electronic surveillance systems to identify associated adverse events and other drug use problems; or
- FDA to increase its surveillance of available data sources, such as registries and administrative and clinical databases, to identify patterns of off-label use and evidence suggesting effectiveness and associated adverse events.

Dissemination. Because some information may be valuable to clinicians and entities that influence prescribing decisions (such as insurers and pharmacy and therapeutics committees), Congress could allow manufacturers to disseminate information about off-label uses that they have developed or of which they are aware, perhaps subject to certain limitations or accompanying reporting requirements. Possibilities include

- broader sharing of clinical analyses of off-label use with coverage deciders (e.g., CMS, insurers, pharmacy and therapeutics committees) to support requests that they cover a particular use of the drug; and
- dissemination of clinical analyses of off-label use at clinical and pharmaceutical conferences.

Oversight. With an estimated 12% to 38% of all prescriptions' (and 56% of oncology prescriptions') being written for uses not listed on FDA-approved labeling,[35] valid information on the extent of off-label use and the effect of such use on manufacturer, insurer, and clinician behavior could potentially better inform debate on how to best protect the public's health. Congress could direct

- the Government Accountability Office (GAO) to study the extent of off-label use in government-provided care (e.g., Department of Veterans Affairs, Bureau of Prisons, and Indian Health Service) and in government-funded care (e.g., Medicare and Medicaid);
- the Secretary of Health and Human Services (HHS) to contract with the National Academy of Medicine or a similar organization to assemble management or industrial policy experts to study the costs and rewards to industry of off-label prescriptions; or

[35] David C. Radley, Stan N. Finkelstein, and Randall S. Stafford, "Off-label Prescribing Among Office-Based Physicians," Archives of Internal Medicine, vol. 166, May 8, 2006; Tewodros Eguale, David L. Buckeridge, Aman Verma, Nancy E. Winslade, Andrea Benedetti, James A. Hanley, Robyn Tamblyn, "Association of Off-label Drug Use and Adverse Drug Events in an Adult Population," *JAMA Internal Medicine*, vol. 176, no. 1, January 2016, https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2467782; W. David Bradford, John Turner, and Jonathan W. Williams, "Off-Label Use of Pharmaceuticals: A Detection Controlled Estimation Approach," presentation at the Innovation and Behavior in Health Markets Conference, 2016, revised May 24, 2018, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2230976; Michael B. Shea, Mark Stewart, Hugo Van Dyke, Linda Ostermann, Jeff Allen, and Ellen Sigal, "Outdated Prescription Drug Labeling: How FDA-Approved Prescribing Information Lags Behind Real-World Clinical Practice," Therapeutic Innovation & Regulatory Science, vol. 52, issue 6 (first published online March 5, 2018; issue published November 1, 2018), https://www.focr.org/sites/default/files/pdf/FOCR-Labeling-Research-Article.pdf?eType=EmailBlastContent&eId=067b86ca-de59-4767-86ab-8a4ad95a7978; abstract at https://journals.sagepub.com/doi/full/10.1177/2168479018759662.

- FDA and the Federal Trade Commission to investigate drugs whose off-label prescriptions account for a particularly high percentage of all prescriptions or that generate a particularly high percentage or high dollar value of sales.

Pricing. The decision to use a drug off-label based solely or primarily on price introduces a new element to study. For example, the pricing difference between Avastin and Lucentis, both made by the same manufacturer with the same active ingredient, is so large that many ophthalmologists use the lower priced Avastin in their treatment of macular degeneration, despite its being an off-label use.[36] The manufacturer included the treatment of macular degeneration in its application to FDA for Lucentis. To explore the ramifications of a traditionally nonclinical element in prescribing decisions, Congress could require

- the HHS Secretary to study the relationship among pricing, access, and prescribing and its effect on patient safety.

Reimbursement. Although FDA approval of a drug—not for each use of a drug—is a requirement for sale in the United States, the decision to reimburse a physician or patient for a drug is made by entities such as the CMS and private insurers. Such decisions, therefore, influence what drugs are prescribed and, in part, for what uses drugs are prescribed. Congress could direct

- the HHS Secretary to study such coverage decisions or to contract with the National Academy of Medicine or a similarly equipped entity to do so; or
- HHS to form a task force to include CMS and FDA, along with private insurers and others involved in coverage decisions, and patient and clinician groups representing those affected by coverage decisions, to identify areas in need of action and to recommend steps in those directions.

Congress also could encourage

- payors to require safety and effectiveness evidence before covering off-label uses.

Research. The traditional path toward adding an indication (reason for use) to the labeling of a drug already approved for other uses has been for the sponsor of the drug to conduct clinical trials and submit a supplemental new drug application (NDA) to FDA. The widespread extent of off-label use suggests that relying on that model is not helping prescribers get better information. Congress could consider

- assigning responsibility (and funding) to the National Institutes of Health and the Patient-Centered Outcomes Research Institute for safety and effectiveness evaluations of off-label uses; or
- requiring, for a drug that has substantial (to be defined) off-label sales, that the manufacturer[37] fund studies, such as clinical trials, to assess the safety and effectiveness of the drug for the off-label use and submit evidence to the HHS Secretary. Depending on the Secretary's assessment of the evidence, the Secretary could request that the manufacturer amend the drug's labeling either to

[36] Kierstan Boyd, "What Is Avastin?" American Academy of Ophthalmology, May 17, 2018, https://www.aao.org/eye-health/diseases/amd-macular-degeneration.

[37] For drugs on patent, this would be the brand-name sponsor of the new drug application (NDA). For drugs no longer on patent that are only marketed as generic products, this would be the holder of the abbreviated NDA. For a description of the regulation of generic drugs, see CRS Report R44703, *Generic Drugs and GDUFA Reauthorization: In Brief*.

add the off-label use to the label as an approved use or to add a statement that clinical evidence does not support the safety and effectiveness of the drug for the off-label use.

Research transparency. FDA regulations describe standards for the design and analysis of clinical trials that a sponsor uses in an NDA. Studies done by or for the manufacturer or by other groups or individuals are not always made public, in which case their findings cannot be reviewed and evaluated. Because the results of such studies may be used in support of off-label uses, by providing positive and negative incentives, Congress could consider requiring or encouraging

- prospective posting of the designs and statistical plans of studies of off-label uses; or
- public reporting of studies of off-label use.

Clinical guidance. Professional societies and other clinical groups often supplement the information available to prescribers from FDA-approved labeling, medical journals, and information from manufacturers. They can issue guidelines and recommend best practices. Congress could engage such groups and encourage

- professional societies to develop evidence-based clinical guidelines and training regarding off-label use.

Precedents from other countries. The United States is not alone in facing the health care and economic implications of off-label use. For example, the member countries of the European Union have addressed measures involving reimbursement, guidance for prescribers, professional standards, and informed consent.[38] Congress could require

- HHS to contract with the National Academy of Medicine or a similarly equipped entity to review measures taken by the European Union and other regulatory bodies and recommend legislative or administrative actions as appropriate.

Concluding Comments

Concerns over off-label use overlap with questions raised by some legislators and regulators in other contexts. In addition to clearly related issues such as what is allowable information in direct-to-consumer advertising, promotion to clinicians, and material shared with payors and insurers, off-label use also affects the entire basis of FDA regulation of drugs through its authority to approve drugs. That means it directly or indirectly affects research, clinical innovation, transparency, patents and exclusivities, pricing, and access.

Changes in law or regulation in any one area may have benefits in some areas and drawbacks in others. For example, FDA's initiative to encourage research in drugs used traditionally but never reviewed and approved by FDA—so-called legacy drugs—stems from its desire for evidence of safety and effectiveness.[39] Such evidence helps protect patients from possible use of ineffective,

[38] Zachary Brennan, "New Report Investigates Drivers of Off-Label Prescribing in the EU," Regulatory Focus, March 3, 2017.

[39] FDA, Unapproved Drugs Initiative, https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/SelectedEnforcementActionsonUnapprovedDrugs/ucm118990.htm Guidance for FDA Staff and Industry, and FDA "Marketed Unapproved Drugs—Compliance Policy Guide Sec. 440.100 Marketed New Drugs without Approved NDAs or ANDAs," September 19, 2011, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070290.pdf.

unsafe, or misdosed drugs. That initiative, in turn, helps enable sponsors to conduct the clinical trials, submit new drug applications, obtain regulatory exclusivity with the new drug approval—and then raise the price of the new branded product while expecting FDA to honor the exclusivity and block the sale of the drug by others. For example, clinicians had been prescribing a compounded version of progestin for use in preventing preterm delivery. Such use had never been adequately tested in clinical trials. One company conducted those trials, and FDA approved its new drug application. The initial price for the new drug, Makena, was $30,000 for a 20-week course; patients had been paying pharmacists $200-$400 for the same course.[40] Unanticipated price increases can also arise from the apparent following of FDA procedures. For example, a new owner of the FDA-approval of an old antiparasitic generic drug raised the price from $14 per tablet to $750, Daraprim's initial price.[41] Such sudden and large price increases become a barrier to patient access and, therefore, a potential threat to health.

In the case of off-label prescribing, actions in any direction—whether by Congress, FDA, or the courts—could have both intended and unanticipated effects. Actions to limit off-label prescribing could have the intended effects of reducing safety risks and the economic cost of using drugs ineffective for their prescribed purposes. Such limits, however, could also stifle informed clinical exploration. Similarly, incentives to mount clinical trials needed to add an indication to the label could help identify and disseminate information on dosing and contradictions. Such incentives, however, could also hurt. For example, a brand drug that added a new indication to its labeling could prevent, through exclusivities, generics from similarly modifying their labeling. Patients could need to pay more.

The recent debates over the right-to-try movement regarding use of investigational drugs by terminally ill patients[42] may preview discussion about any proposed restrictions on off-label use. The Goldwater Institute, considered a key impetus to development and passage of the 2018 enactment of a right-to-try act,[43] looks to diminish government's role in an individual's choice and has supported dissemination of off-label information.[44]

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[40] Joanne Armstrong, "Unintended Consequences—The Cost of Preventing Preterm Births after FDA Approval of a Branded Version of 17OHP," *New England Journal of Medicine,* online March 16, 2011; and Gardiner Harris, "Drugs' Cost and Safety Fuel a Fight," *New York Times,* April 4, 2011, https://www.nytimes.com/2011/04/05/health/05FDA.html?rref=collection%2Fbyline%2Fgardiner-harris&action=click&contentCollection=undefined&region=stream&module=stream_unit&version=search&contentPlacement=1&pgtype=collection. The compounded version of the drug continues to be available for indications other than prevention of prematurity. FDA has not actively sought to stop sales. See Yesha Patel and Martha M. Rumore, Controversies in Practice "Hydroxyprogesterone Caproate Injection (Makena) One Year Later: To Compound or Not to Compound—That Is the Question," P&T, vol. 37 no. 7, July 2012, pp. 405-411, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3411212/pdf/ptj3707405.pdf, and FDA, "Questions and Answers on Updated FDA Statement on Compounded Versions of hydroxyprogesterone caproate (the active ingredient in Makena)," Press Announcement, Page Last Updated: 06/29/2012, http://wayback.archive-it.org/7993/20170113105722/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310215.htm.

[41] Andrew Pollack, "Drug Goes From $13.50 a Tablet to $750, Overnight," *New York Times,* September 20, 2015, https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html.

[42] CRS Report R45414, *Right to Try: Access to Investigational Drugs*.

[43] See, for example, ADI News Services, "Goldwater Institute's Right To Try Bill Signed By California Governor," Arizona Daily Independent, September 29, 2016, https://arizonadailyindependent.com/2016/09/29/goldwater-institutes-right-to-try-bill-signed-by-california-governor/; and Marie McCullough, "For the terminally ill, are 'right-to-try' laws offering a lifeline, or false hope?" *The [Philadelphia] Inquirer*, April 4, 2017, https://www.philly.com/philly/health/Do-Right-to-Try-laws-offer-a-lifeline-or-false-hope-to-the-terminally-ill.html.

[44] Naomi Lopez Bauman, "Restoring Free Speech in Medicine," Goldwater Institute, June 6, 2017, https://goldwaterinstitute.org/article/restoring-free-speech-in-medicine; and Starlee Coleman, "Arizona becomes first state to allow pharmaceutical companies to legally communicate off-label treatment uses to medical professionals," Goldwater Institute, March 23, 2017, https://goldwaterinstitute.org/article/arizona-becomes-first-state-to-allow-

Congress has built a process in which a robust FDA can regulate drugs to protect the public's health. Is there cause for concern that perhaps a third[45] of prescriptions are for off-label uses and that, in at least one study, three-quarters of those had minimal or no accepted scientific evidence to support their use?[46]

Policy tension exists over the line between wanting to ensure individuals' freedom to take drugs for off-label uses and wanting to protect the public from the risk of unsafe or ineffective drugs. Where to draw that line—and how to know when it may be time to move the line—is of continuing interest to regulators and legislators.

pharmaceutical-companies-legally-communicate-off-label-treatment/.

[45] W. David Bradford, John Turner, and Jonathan W. Williams, "Off-Label Use of Pharmaceuticals: A Detection Controlled Estimation Approach," presentation at the Innovation and Behavior in Health Markets Conference, 2016, revised May 24, 2018, https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2230976.

[46] David C. Radley, Stan N. Finkelstein, and Randall S. Stafford, "Off-label Prescribing Among Office-Based Physicians," Archives of Internal Medicine, vol. 166, May 8, 2006.

Appendix. Selected Actions to Expand Information in Drug Labeling

Table A-1. Selected Congressional and FDA Actions to Expand Information in Drug Labeling

Date	Topic	Law or Agency Action
1906	Required that sellers state on a drug's label the "quantity or proportion of any alcohol, opium, …" contained; and considered as "misbranded" any drug whose label was "false or misleading."	Federal Food and Drug Act of 1906 (F&DA), P.L. 59-384
1938	Required that labeling include adequate directions for use and evidence of safety of their labeled use.	Federal Food, Drug, and Cosmetic Act (FFDCA), P.L. 75-717
1962	Would declare as misbranded a prescription drug whose advertising did not adhere to required labeling information.	Kefauver-Harris Drug Amendments to the FFDCA, P.L. 87-781. Sec. 131 added FFDCA Sec. 502(n).
1975	Prohibited manufacturers from advertising and otherwise promoting off-label uses of approved drugs.	21 CFR 202.1, Prescription drug advertisements [40 FR 14016, March 27, 1975]
1977–2003	FDA issued a 1977 guidance and a 1998 rule, and Congress took up related efforts in 2002 and 2003 to both require and encourage manufacturers to conduct the research to support adequate labeling concerning the use for children of approved drugs.	FDA, "Guidance for Industry: General Considerations for the Clinical Evaluation of Drugs in Infants and Children," September 1977, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071687.pdf; FDA, "Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final rule," Federal Register, vol. 63, no. 231, December 2, 1998, pp. 66632-66672; Best Pharmaceuticals for Children Act (BPCA, P.L. 107-109); and Pediatric Research Equity Act (PREA, P.L. 108-155).
1993	Added Medicare coverage of off-label cancer drug use, by defining "medically accepted indication" as, for an FDA-approved drug, a use included in a cited compendia or other Secretary-defined compendia or which the carrier determines is acceptable based peer-reviewed supportive clinical evidence according to guidance from the Secretary.	P.L. 103-66 amended the Social Security Act Sec. 1861(t)(2)(B) [42 U.S.C. 1395x].
1993–2007	FDA issued "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs." Directed the Secretary of Health and Human Services to review and develop guidance on including women and minorities in clinical trials, which would make appropriate labeling possible.	FDA, "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs," Federal Register, Vol. 58, No. 139, July 22, 1993. FDA Modernization Act of 1997 IFDAMA), P.L. 105-115
2006	Required that labeling include highlights of prescribing information to help health care providers use the information.	"Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products," referred to as the "Physician Labeling Rule," 71 FR 3922, January 24, 2006, 21 CFR 201.56 and 201.57.

Date	Topic	Law or Agency Action
2007	Authorized the Secretary, upon learning of new relevant safety information, to require a labeling change.	FDA Amendments Act of 2007, P.L. 110-85. See FFDCA 505(o).
2012	Directed the Secretary of Health and Human Services to assess the extent to which demographic subgroups (to include sex, age, race, and ethnicity) participate in clinical trials and are included in safety and effectiveness data submitted in marketing applications. It also required the Secretary to publish an action plan with recommendations to improve the completeness, quality, and inclusion of subgroup data in various analyses. Such information could then be reflected in a drug's labeling.	FDA Safety and Innovation Act (FDASIA), P.L. 112-144
2014	Required that labeling include a summary of the risks of using a drug during pregnancy and lactation	"Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling," referred to as the "Pregnancy and Lactation Labeling Rule," 79 FR 72063, December 4, 2014.
2016	Required FDA to establish a program to evaluate the use of real world evidence (RWE) to support approval of a new indication for an already approved drug.	Section 3022 of the 21st Century Cures Act, P.L. 114-255

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