



More Transparency Needed to Ensure Medicaid Beneficiaries Have Access to Necessary Off-Label Prescription Drugs

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Under federal law, state Medicaid programs are required to cover (with a few exceptions) outpatient prescription drugs for “medically accepted indications.”¹ Medically accepted indications are both those that are included on the drug’s label by the FDA as part of the approval process, and certain “off-label” uses.² FDA regulations require drug labels to provide “a summary of the essential scientific information needed for the safe and effective use of the drug.”³ Labels are required to provide several categories of information including indications and usage, dosage forms and strength, and adverse interactions.⁴ The information included on a drug’s label is based on the drug’s approval by the FDA, which in turn is informed by clinical trials, animal research, and other data about the drug submitted to the FDA by the manufacturer.⁵ Any prescription for a drug that deviates from what is on the FDA-approved label, such as a prescription to treat a condition other than those listed on the label, or a prescription for a different dosage, is considered an “off-label” use.⁶

Under federal law, state Medicaid programs are required to apply a uniform statutory standard when deciding which outpatient drugs they must cover. The uniformity is an important beneficiary protection because it prevents various and conflicting standards from one state to

¹ 42 U.S.C. § 1396r-8(d)(1)(B)(i).

² *Id.* § 1396r-8(k)(6).

³ 21 C.F.R. § 201.56(a)(1).

⁴ *Id.* § 201.56(d)(1).

⁵ U.S. Food & Drug Admin., *Understanding Unapproved Use of Approved Drugs "Off Label"* (2018), <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label>.

⁶ *Id.*

the next.⁷ However, as discussed below, because of the limits of the existing system of coverage for off-label uses, Medicaid outpatient drug benefit coverage of off-label uses is not always as uniform as intended.

Off-label uses

There are many reasons a use for a particular drug, even a common use, may not make it onto the FDA-approved label. For example, few clinical drug trials include children or pregnant people, so drug labels often exclude children and pregnant people, though the drugs may be prescribed to these populations to treat the same conditions for which they are used in non-pregnant adults.⁸ Off-label uses are also common to treat rare diseases, for which there is no FDA-approved treatment or to treat conditions after someone has exhausted all FDA-approved treatment options.⁹ In these cases, it may not be possible for a drug manufacturer to gather the volume and type of documentation needed to obtain FDA approval to make that particular use of the medication “on label.”¹⁰ In addition, the FDA process to update a drug’s labeling can be slow and expensive, discouraging drug manufacturers from submitting additional uses of an already approved drug for inclusion on the label. There is often little financial benefit to the manufacturer of expanding the approved uses on the label.¹¹ Given these considerations, it is no surprise that “off-label” prescriptions are quite common in the U.S., comprising about one-fifth of all prescriptions.¹²

⁷ See, e.g. *Edmonds v. Levine*, 417 F. Supp. 2d 1323, 1338 (S.D. Fla. 2006); *Ark. Dep’t Hum. Servs. et al. v. Sarepta*, 2021 Ark. App. 330, 333 (Ark. Ct. App. 2021).

⁸ Christopher M. Wittich, et al, *Ten Common Questions (and Their Answers) About Off-label Drug Use*, 7 Mayo Clinic Proc. 982, 984 (2012).

⁹ U.S. Food & Drug Admin., *supra* note 5.

¹⁰ Wittich, et al, *supra* note 8 at 986. Special procedures do allow manufacturers to forgo some of the usual requirements to obtain FDA approval for “orphan drugs” to treat extremely rare conditions. See *id.*; 21 U.S.C. §§ 360aa-360ee; 26 U.S.C. § 45C.

¹¹ Wittich, et al, *supra* note 8 at 987.

¹² Agency Health Qual. & Res., Off-Label Drugs: What You Need to Know,

<https://www.ahrq.gov/patients-consumers/patient-involvement/off-label-drug-usage.html> (last visited Jan. 7, 2022).

Medicaid coverage of off-label drugs

The Medicaid program requires broad coverage of prescription medications for drugs approved by the FDA. However, Medicaid programs are mandated only to cover these drugs for their FDA-labeled indications and certain off label indications.¹³ Medicaid programs are only required to cover off label prescriptions when their use “is supported by one or more citations included or approved for inclusion in” at least one of the three compendia listed in the statute.¹⁴ The listed compendia are the American Hospital Formulary Service Drug Information; United States Pharmacopeia-Drug Information (or its successor publications); and the DRUGDEX Information System.¹⁵ Notably, while three compendia are listed in the statute, United States Pharmacopeia-Drug Information is no longer available.¹⁶ DrugPoints was recognized as a successor to United States Pharmacopeia-Drug Information in Medicare for off-label cancer therapies for a time, but CMS stopped recognizing it as a compendia for that purpose in 2008, finding that it was “not an authoritative compendium.”¹⁷ CMS has not weighed in on whether DrugPoints is still considered a successor to United States Pharmacopeia-Drug Information for Medicaid, and as a result, there is variation in state recognition of DrugPoints as a compendia for the purposes of determining off-label coverage in Medicaid.¹⁸

¹³ 42 U.S.C § 1396r-8(k)(2).

¹⁴ *Id.* § 1396r-8(k)(6).

¹⁵ *Id.*; see also Ctr. Medicare Advocacy, *Medicare Coverage for Off-Label Drug Use* 4-5 (2010), <https://medicareadvocacy.org/cma-report-medicare-coverage-for-off-label-drug-use> (describing the compendia).

¹⁶ See Amy P. Abernethy et al., *Systematic Review: Reliability of Compendia Methods for Off-Label Oncology Indications*, 150 *Ann. Int. Med.* 336, 339 (2009).

¹⁷ Ctrs. Medicare & Medicaid Servs., *Thomson Micromedex DrugPoints Compendium Revision Request - CAG-00390* (2008), <https://www.cms.gov/medicare-coverage-database/view/medicare-coverage-document.aspx?MCDId=15>. IBM acquired the rights to DrugPoints in 2016, further muddying the waters as to whether it may still be recognized as a successor publication to United States Pharmacopeia-Drug Information for any purpose.

¹⁸ *E.g.*, compare Nevada Medicaid, *High Dollar Claim Prior Authorization Request Form 1* (2019), <https://www.medicaid.nv.gov/Downloads/provider/FA-159.pdf> (DrugPoints not a recognized compendia for off-label uses in Nevada Medicaid), with Select Health South Carolina, *Pharmacy Prior Authorization Criteria* 214 (2022), <https://www.selecthealthofsc.com/pdf/provider/resources/pa-criteria.pdf> (DrugPoints may be considered when determining whether an off-label use is covered in South Carolina Medicaid).

Putting aside the question of which compendia can be used to determine off-label coverage, there is also the question of what it means to be supported by citation in one of the compendia. As one court has stated:

[T]he Medicaid Act directs a state Medicaid agency to determine if a prescription is for a “medically accepted indication” by examining the text of the congressionally-approved drug compendia (if not for an FDA-approved use). If the use is supported by a citation in any of the compendia, as the statute mandates, then the state must cover the prescription. This examination. . . leaves no room for the exercise of discretion on the part of the state agency to determine its own criteria for defining whether and how a use is supported by citation. The statute as written eliminates such discretion and results in a single, nationally uniform list of medically accepted indications.¹⁹

Another court recently found that the statute “includes those off-label uses for which an approved medical compendium tends to show or helps prove the efficacy and safety of the prescribed off-label use.”²⁰

Medicaid beneficiaries face barriers to off-label uses

Unfortunately, these compendia are not only difficult for laypeople to access, but they are also geared toward a clinical audience.²¹ Thus, for the average Medicaid beneficiary (or their advocates) determining whether the particular off-label use of a drug must be covered by Medicaid is extremely difficult.

For one, the compendia are not free. A one year, single use subscription to American Hospital Formulary Service Drug Information starts at \$84.²² DrugDEX and DrugPoints are currently

¹⁹ *Edmonds*, 417 F. Supp. 2d at 1325; *see also id.* (discussing of what it means to be supported by citation for each of the listed compendia).

²⁰ *Dobson v. Sect’y Health & Hum. Servs.*, No. 20-11996, 2022 WL 424813 at *1 (Feb. 11, 2022 11th Cir.).

²¹ *See* Ctr. Medicare Advocacy, *supra* note 15 at 5-8 (though this report describes issues for Medicare beneficiaries, the Medicare statute references the same three compendia in the Medicaid statute, so the issues significantly overlap).

²² AHFS-DI, AHFS Clinical Drug Information,

<https://www.ahfsdruginformation.com/ahfs-clinical-drug-information/> (last visited Mar. 8, 2022).

owned by IBM and are not generally available for purchase by members of the public. Subscribers generally consist of hospitals, medical libraries, and doctor's offices. According to IBM, subscriptions are priced according to a tiered system based on the features associated with the subscription and whether the subscriber bundles the subscription with other services offered by IBM.²³ IBM does not publish its pricing for these products.²⁴ IBM does, however, publish a publicly available summary of the information in DrugDex through its app, "Mobile Micromedex® Drug Ref," which is currently available for an annual subscription of \$2.99.²⁵ In addition to their cost, the compendia are not readily accessible in public places like libraries.²⁶ Further, the compendia are designed for a clinical audience and are not easy to navigate for lay people or non-clinical advocates.²⁷

In addition, the compendia are controlled by private entities who may rely on the funds they receive from pharmaceutical companies, raising questions about potential conflicts of interest. AFHS touts itself as "the only remaining official drug compendium published by a non-commercial entity (*i.e.*, by a tax-exempt ["nonprofit"] professional association)."²⁸ It is published by the American Society of Health-System Pharmacists, a 501(c)(6) tax-exempt organization, under the authority and oversight of its Board of Directors.²⁹ In 2019, the American Society of Health-System Pharmacists reported revenues of over \$56 Million, and assets of over \$160 million.³⁰ IBM, the current owner of DrugDex and DrugPoints, is a publicly

²³ IBM, IBM Micromedex with Watson Bundles, <https://www.ibm.com/products/micromedex-with-watson/pricing> (last visited Mar. 8, 2022); TDS Health, DrugPoints® System,

<https://www.tetondata.com/TitleInfo.cshtml?id=6> (last visited Apr. 5, 2022).

²⁴ IBM, *supra* note 23; TDS Health, *supra* note 23.

²⁵ See, e.g., Efficient MD, *The Best Emergency Medicine Apps in 2021* (Jan. 5, 2021), <https://efficientmd.com/the-best-emergency-medicine-apps/>.

²⁶ See Ctr. Medicare Advocacy, *supra* note 15 at 6-7.

²⁷ See Ctr. Medicare Advocacy, *supra* note 15 at 7-8.

²⁸ AHFS Clinical Drug Info., Editorial Independence, <https://www.ahfsdruginformation.com/editorial-independence> (last visited Mar. 9, 2022).

²⁹ AHFS Clinical Drug Info., *supra* note 28.

³⁰ ProPublica, Nonprofit Explorer: American Society of Health-System Pharmacists, <https://projects.propublica.org/nonprofits/organizations/520807628> (last visited Mar. 9, 2022).

traded company, currently ranked 42 on the Fortune 500, and reported over \$73 Billion in revenues in 2020, and over \$155 Billion in assets.³¹

While both statutory compendia have conflict of interest protections in place, neither the statute nor guidance set standards for conflicts of interest for compendia, providing their publishers with wide latitude in this respect.³² For example, while the compendia exclude people from authoring or reviewing recommendations for inclusion in the compendia based on financial relationships with drug manufacturers when they surpass a certain threshold, one study surmised: “When names of authors or consensus committee members are provided for compendia listings (which they often are not), financial relationships with industry frequently are apparent.”³³ Further, the conflict of interest policies of the compendia vary considerably.³⁴

Moreover, each compendia has its own process for receiving, considering, and deciding on requests to recommend an off-label indication. Yet for all compendia, external requests come from interested parties, often drug manufacturers.³⁵ As one study noted, “drug manufacturers interact with compendia developers and can lobby for indications to be added or altered.”³⁶ The internal processes for developing compendia recommendations are generally not open to the public.³⁷ As a result, any potential conflicts of interest will be difficult for outsiders to notice or understand.

³¹ Fortune, Fortune 500: IBM, <https://fortune.com/company/ibm/fortune500> (last visited Mar. 9, 2022).

³² See Angela K. Green et al., *Time to Reassess the Cancer Compendia for Off-label Drug Coverage in Oncology*, 316 J. Am. Med. Ass’n 1541, 1541 (2016); Ross McKinney et al., Ag. Health Care Qual. & Res., *White Paper: Potential Conflict of Interest in the Production of Drug Compendia* (2009), <https://www.ncbi.nlm.nih.gov/books/NBK253242>.

³³ Green et al., *supra* note 32 at 1542.

³⁴ *Compare* AFHS Clinical Drug Info., Conflict of Interest and Disclosure Policy, <https://www.ahfsdruginformation.com/conflict-of-interest-and-disclosure-policy> (last visited Mar. 9, 2022) *with* IBM, *Conflict of Interest Policy for IBM Micromedex* (2019), <https://www.ibm.com/downloads/cas/8WBZ9KAJ>.

³⁵ Katherine Tillman et al., *Compendia and Anticancer Therapy Under Medicare*, 150 Annals Int. Med. 348, 349 (2009).

³⁶ Green et al., *supra* note 32 at 1542.

³⁷ Tillman et al., *supra* note 35 at 349; Dep’t Health & Hum. Servs., *OIG Memorandum Report: Drug Compendia Publishers Maintain Transparent Processes for Evaluating Anticancer Drug Therapies and Identifying Potential Conflicts* (2014), <https://oig.hhs.gov/oei/reports/oei-07-13-00220.pdf>. As discussed in more detail

Moreover, there is no guarantee that the compendia are up-to-date with current clinical practice or even evidence-based practice. More than a decade ago, the Agency for Health Care Quality Research sounded this alarm, noting that the compendia were “unable to keep up with new evidence in order to maintain a timely, comprehensive source of information for practitioners.”³⁸

Unfortunately, over the intervening years, the situation has not greatly improved. One recent study found that more than two-thirds of the current evidence-based off-label uses in dermatology were not included in the compendia, and concluded: “[T]reatment options listed in these compendia are incomplete, outdated, idiosyncratic, and unpredictable. To ensure that patients can access treatments for their disease, it appears that policies to reduce the reliance on these compendia for coverage determinations should be developed.”³⁹ The study noted that the compendia not only omitted several “common, first-line, evidence-based treatments,” but also that “many cost-effective therapies were excluded from these compendia, thus limiting access to their use.”⁴⁰

Another study looked at off-label transplant immunosuppressants, noting that these medications are “often used off-label because of insufficient randomized prospective trial data to achieve organ-specific US Food and Drug Administration (FDA) approval.”⁴¹ That study similarly found that the compendia failed to include several established off-label uses, concluding that there is “a substantial gap between what is considered standard of care for transplant recipients” and the uses listed in the compendia.⁴² Given the fact that the compendia are not regularly updated and often do not contain well-established and evidence-

below, designated compendia for Medicare anti-cancer therapies must make some information about their processes and conflicts of interest publicly available. *See id.*

³⁸ Surrey M. Walton et al., Ag. Health Care Qual. & Res., *Developing Evidence-Based Research Priorities for Off-Label Drug Use* 9 (2009),

https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/off-label-use-research-priorities_research.pdf.

³⁹ John S. Barbieri et al., *Evaluation of Clinical Compendia Used for Medicare Part D Coverage Determinations for Off-label Prescribing in Dermatology*, 155 JAMA Derm. 315, 315 (2019).

⁴⁰ *Id.* at 319.

⁴¹ Lisa M. Potter et al., *Transplant Recipients are Vulnerable to Coverage Denial Under Medicare Part D*, 18 Am. J. Transplantation 1502, 1502 (2018).

⁴² *Id.* at 1509.

backed off-label uses, Medicaid programs may exclude these off-label uses from coverage, leaving beneficiaries without recourse to access them.

Moreover, the inaccessibility of the compendia raises serious transparency issues, since beneficiaries will be hard-pressed to determine whether an off-label use their provider has recommended must be covered. “The net result of this system is the abdication of treatment choice from physicians and insurers to unregulated and unaccountable third parties. Improved transparency around compendia development and update cycles is necessary to clarify decision making.”⁴³ This, in turn, leads to potential due process issues, since a beneficiary often has no meaningful way to contest a Medicaid program’s refusal to cover an off-label use by showing that it is supported in at least one of the compendia.

Due process concerns with Medicaid off-label drug access

These transparency issues are particularly important when Medicaid programs deny coverage of off-label drugs. The Medicaid Act and the U.S. Constitution both provide for procedural due process rights including prior notice when an individual is denied benefits to which they are entitled, including medical care. The Supreme Court has interpreted the Constitution’s due process protections to require “timely and adequate notice detailing the reasons for a proposed” adverse decision.⁴⁴ The federal Medicaid regulations have also codified notice requirements when request for Medicaid covered services “is denied or is not acted upon with reasonable promptness.”⁴⁵

The notice must contain a statement of the intended action, specific legal support for the action, and an explanation of the individual’s appeal and hearing rights, and right to continued benefits.⁴⁶ As one court stated, constitutional notice must, at a minimum, “explain, in terms comprehensible to the claimant, exactly what the agency proposes to do and why the agency is taking this action.”⁴⁷ Where a Medicaid program denies an off-label use, however, the beneficiary does not have true access to the reason for the denial when beneficiaries have no effective way to confirm whether the off-label use they are seeking is supported by citation in one of the statutory compendia.

⁴³ Barbieri et al., *supra* note 39 at 318.

⁴⁴ *Goldberg v. Kelly*, 397 U.S. 254, 267-68 (1970).

⁴⁵ 42 U.S.C. § 1396a(a)(3).

⁴⁶ 42 C.F.R. §§ 431.210 (fee for service), 438.404(b) (managed care).

⁴⁷ *Ortiz v. Eichler*, 616 F. Supp. 1046, 1061 (D. Del. 1985), *aff’d*, 794 F.2d 889 (3d Cir. 1986).

Reform efforts to make Medicaid compendia more accessible

Advocates are working to make the compendia more transparent so that beneficiaries and providers know which off-label uses must be covered and have the information they need to contest denials of off-label medications. Congress is beginning to take notice. Notably, Medicare Part D also relies on compendia to determine the scope of drugs and biologicals used off-label, incorporating by reference the definition of “medically accepted indication” in the Medicaid Act.⁴⁸ There, however, the Medicare Act also allows off-label uses for anticancer drugs to be supported by “other authoritative compendia as identified by the Secretary.”⁴⁹ In 2008, after significant public attention to the limits of the statutory compendia with respect to cancer treatment, the statute was amended by the Medicare Improvements for Patients and Providers Act (MIPPA) to specify that, for anticancer drugs, “no compendia may be included on the list of compendia under this subparagraph unless the compendia has a publicly transparent process for evaluating therapies and for identifying potential conflicts of interests.”⁵⁰ Federal regulations and guidance set forth the process for considering new compendia for anticancer drug treatments, and flesh out the criteria for potential compendia.⁵¹

Medicare currently recognizes five compendia for off-label anticancer uses: American Hospital Formulary Service-Drug Information (AHFS-DI), National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium, Truven Health Analytics Micromedex DrugDEX, Elsevier/Gold Standard Clinical Pharmacology, and Wolters Kluwer Lexi-Drugs.⁵² The changes in Medicare have also resulted in considerably more information about off-label uses for medications used to treat cancer that is free and publicly available online, while similar

⁴⁸ 42 U.S.C. § 13952w-102(e)(4).

⁴⁹ *Id.* § 1395x(t)(2)(B)(ii).

⁵⁰ *Id.* § 1395x(t)(2)(B)(ii); see generally CMS, *Pub 100-02 Medicare Benefit Policy, Transmittal 120* (Jan. 29, 2010), <https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R120BP.pdf> (discussing the changes implemented by MIPPA); Jean D. LeMasurier & Babette Edgar, *MIPPA: First Broad Changes to Medicare Part D Plan Operations*, 2 *Am. Health Drug Ben.* 111 (2009).

⁵¹ 42 C.F.R. § 414.930.; Ctrs. Medicare & Medicaid Servs., *Pub 100-02 Medicare Benefit Policy, Transmittal 120* (Jan. 29, 2010), <https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/Downloads/R120BP.pdf>.

⁵² Ctrs. Medicare & Medicaid Servs., *Pub 100-02 Medicare Benefit Policy, Transmittal 212* at 3 (Nov. 6, 2015), <https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/R212BP.pdf>.

information for other off-label uses remains behind paywalls, inaccessible to the general public.

Recommendations

The Medicaid Act's reliance on the three compendia to determine the scope of coverage for off-label prescriptions raises serious concerns about whether Medicaid beneficiaries have access to the medications they need.

State Medicaid Programs should

- Include the relevant compendia sections with any denial notices showing that the state verified that the prescribed use is an unsupported off-label use.
- Operate a hotline or provide other support to clinicians and Medicaid enrollees seeking information on whether a prescribed use is supported by citation in the compendia.

CMS should

- Establish conflict of interest protections and transparency requirements for the compendia, including limits on who is making recommendations and whether they receive funds from the manufacturer in question.
- Provide for public access to the compendia to ensure that Medicaid enrollees can access the outpatient prescription drugs as required by federal law.

Congress should

- Amend the Medicaid Act to provide the Secretary of HHS with the authority to designate other compendia as allowable to determine the scope of acceptable off-label uses, when they meet criteria for transparency, conflict-of-interest avoidance, and accessibility.
- Establish a federal body that reviews off-label uses and makes recommendations for coverage in public programs based on peer-reviewed literature, and existing standards of care and evidence based practice. The process should be transparent, accountable, and timely.