NATIONAL HEALTH COUNCIL

June 11, 2026

Acting Commissioner of Food and Drugs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Drug Repurposing for Unmet Medical Needs; Request for Information [FDA-2026-N-4492

Submitted via regulations.gov

Dear Acting Commissioner:

The National Health Council (NHC) appreciates the opportunity to provide comments in response to the Food and Drug Administration's (FDA's) Request for Information (RFI) on drug repurposing for unmet medical needs. The RFI raises important questions about how FDA, in coordination with federal partners and external stakeholders, can better identify opportunities to repurpose approved drugs for new uses in areas of significant unmet medical need, particularly where the existing commercial incentives may be insufficient to support the traditional supplemental approval pathway. These questions are especially relevant to patients and caregivers in disease areas where therapeutic options are limited and evidence may be fragmented across clinical practice and published literature. Patients may also face uncertainty regarding whether uses of repurposed drugs are supported by adequate evidence, reflected in labeling, and accessible through coverage.

Created by and for patient organizations more than 100 years ago, the NHC convenes organizations from across the health ecosystem to forge consensus and drive patient-centered health policy. We promote increased access to affordable, high-value, comprehensive, accessible, and sustainable health care. Made up of nearly 200 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient organizations. Other members include health-related associations and nonprofit organizations including the provider, research, and family caregiver communities; and businesses and organizations representing biopharmaceuticals, devices, diagnostics, generics, and payers.

The NHC supports FDA's effort to examine how drug repurposing can help address unmet medical needs, provided that such efforts are grounded in sound evidence, transparent decision-making, and meaningful patient engagement. Drug repurposing may offer important opportunities where an approved product's known safety profile, accumulated clinical experience, mechanistic rationale, or emerging evidence suggests potential benefit in a new use. In some cases, repurposing may allow patients to benefit from therapies that are already manufactured, familiar to clinicians, and supported existing scientific or clinical evidence. At the same time, the NHC urges FDA to ensure

repurposing strengthens patient-centered evidence development and labeling without weakening the standards patients rely on to distinguish evidence-based care from unsupported claims.[1,2]

For patients, the value of drug repurposing depends not only on identifying potential new uses, but also on ensuring that evidence supporting that use is reliable, labeling is updated when appropriate, clinicians and patients receive clear information, and coverage and access barriers are addressed. A therapy that appears promising in the literature but remains absent from labeling, inconsistently reflected in guidelines or compendia, and subject to coverage denials may provide limited real-world benefit.[3,4] Conversely, a repurposing process that updates labeling without adequate patient engagement, clear communication, or attention to access may fail to resolve the practical barriers that patients experience when seeking care.

Summary of Recommendations

The NHC therefore encourages FDA to use this RFI to inform how a coordinated, patient-centered approach to drug repurposing could better identify high-priority opportunities, clarify evidence needs, and address practical barriers for patients. Such a framework should recognize the distinct but complementary roles of FDA, the National Institutes of Health (NIH), the Centers for Medicare & Medicaid Services (CMS), patient organizations, clinicians, academic researchers, manufacturers, and payers. FDA is appropriately focused on the regulatory question of when evidence is sufficient to support a new labeled use. However, the broader value of drug repurposing will depend on whether federal partners and external stakeholders can help identify priority opportunities, generate or synthesize evidence, support clear labeling, reduce avoidable uncertainty for clinicians and patients, and address access barriers once evidence is sufficient. The NHC offers the following recommendations:

- Prioritize repurposing opportunities in disease areas with significant unmet need, limited treatment options, serious health consequences, and meaningful patient-community interest.

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[1] U.S. Food and Drug Administration, *Benefit-Risk Assessment for New Drug and Biological Products: Guidance for Industry* (Silver Spring, MD: FDA, October 2023), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-assessment-new-drug-and-biological-products.

[2] U.S. Food and Drug Administration, "FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making," last modified February 2024, https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical.

[3] John Barbieri et al., "Evaluation of Clinical Compendia Used for Medicare Part D Coverage Determinations for Off-label Prescribing in Dermatology," *JAMA Dermatology* 155, no. 3 (2019): 316, https://doi.org/10.1001/jamadermatol.2018.5052.

[4] Justin Lee et al., "Updated Resource: Commercial Payers' Use of Oncology Compendia," Avalere Health Advisory, November 6, 2025, https://advisory.avalerehealth.com/insights/new-resource-commercial-payers-use-of-oncology-compendia.

- Establish a transparent, patient-informed process for identifying and evaluating repurposing candidates, including clear distinctions among candidates with sufficient evidence, promising clinical signals, and preclinical or computational signals.
- Engage patient organizations early and systematically to identify unmet need, meaningful outcomes, treatment burden, patient tolerance for risk and uncertainty, and real-world barriers to use.
- Maintain rigorous evidentiary standards while using appropriate flexibility, including reliance on well-developed literature reviews, real-world evidence, mechanistic evidence, and externally controlled evidence where scientifically justified.
- Work with federal partners to examine coverage and access barriers that may persist even after a drug has been repurposed or where a medically appropriate off-label use is supported by evidence.
- Coordinate with NIH, CMS, and other federal partners to develop a coordinated federal strategy to support evidence generation, labeling updates, dissemination, understanding of coverage and access implications, and post-labeling monitoring.
- Ensure that repurposing initiatives do not create access barriers, expose patients to unsupported use, or replace the development of new therapies where new treatments are still needed.

Priority Areas for Drug Repurposing

The NHC agrees that the priority areas identified in the RFI, including metabolic diseases, neurodegenerative conditions, women's health conditions, men's health conditions, substance use disorders, and rare diseases, are appropriate starting points for FDA's consideration. These areas include conditions with substantial unmet need, significant patient and caregiver burden, and potential opportunities for repurposing based on accumulated clinical experience, emerging scientific understanding, or existing use of approved therapies in related conditions. The inclusion of rare diseases and neurodegenerative conditions is particularly important because patients and families in these communities often face long diagnostic journeys, limited or no approved treatment options, progressive disability, and substantial uncertainty regarding disease management. In these contexts, even modest improvements in function, symptom burden, disease stabilization, or treatment convenience may be highly meaningful to patients.[5,6]

At the same time, the NHC encourages FDA to avoid treating the initial list of priority areas as exhaustive. A patient-centered repurposing framework should be guided by unmet need, disease burden, strength of evidence, feasibility of evidence generation, and input from patient communities rather than by a predetermined set of disease

[5] U.S. Food and Drug Administration, "FDA Patient-Focused Drug Development Guidance Series."

[6] National Health Council, "Patient Reported Outcomes and Patient Centered Outcomes," Clinical Outcome Assessment Webinar Series, National Health Council, November 2018, webinar, https://nationalhealthcouncil.org/webinars/clinical-outcome-assessment-webinar-series-patient-reported-outcomes-and-patient-centered-outcomes/.

categories. Some high-prevalence conditions may present substantial public health opportunities, but some low-prevalence conditions may involve equally compelling or greater unmet need when measured by severity, lack of alternatives, caregiver burden, and consequences of delayed or ineffective treatment. The NHC therefore encourages FDA to adopt a transparent set of criteria that can be applied across disease areas and allows patient organizations, clinicians, researchers, and other stakeholders to identify opportunities that may not fit neatly within the initial categories listed in the RFI.

In applying such criteria, the NHC recommends that FDA weigh factors such as the seriousness of the condition, the adequacy of existing treatment options, the practical burden on patients and caregivers, the existence of clinically meaningful evidence or plausible biological rationale, the feasibility of generating additional evidence where needed, and the likelihood that a labeling change would improve clinical decision-making or access. The NHC also encourages FDA to consider whether a repurposing opportunity could reduce inappropriate variation in care, clarify uncertainty for clinicians and patients, or improve access for populations whose needs are not well addressed under current labeling. These considerations are particularly important for patients with pediatric-onset disease, older adults, pregnant or postpartum patients, individuals with cognitive impairment, patients with multiple chronic conditions, and medically fragile individuals, all of whom may experience treatment gaps even in disease areas where therapies exist for the general adult population.

The NHC also recommends that the FDA incorporate input from patient organizations to help identify which unmet needs are most urgent and which outcomes are most meaningful. Patients may define benefit differently depending on the condition, disease stage, available alternatives, and burden of treatment. For some communities, a repurposed therapy may be valuable because it improves survival or slows progression. For others, the most meaningful benefit may be improved daily functioning, reduced symptom burden, fewer treatment visits, less invasive administration, improved tolerability, or greater ability to participate in family, school, work, or community life. FDA’s prioritization process should be sufficiently flexible to recognize these differences.

A Patient-Centered Framework for Selecting Repurposing Candidates

The RFI appropriately distinguishes among repurposing candidates for which sufficient evidence may already exist to support a new use, those with preliminary clinical signals that require additional study, and those with preclinical or computational signals that remain hypothesis-generating. The NHC supports these distinctions and encourages FDA to make them central to any public-facing repurposing process. Clear categorization among candidate types is essential to avoid confusion, premature demand, inconsistent prescribing, or payer uncertainty.

Public nominations of individual products can be valuable, particularly when submitted by patient organizations, clinicians, researchers, or disease-specific coalitions with substantial expertise. However, the NHC does not recommend that FDA rely primarily on broad public nominations without a structured method for evaluating evidence quality, patient relevance, feasibility, and access implications. Nominations should be organized through a transparent framework that prevents the process from becoming

inconsistent, duplicative, or overly dependent on the visibility or resources of particular disease communities. A disease community with a small organizational infrastructure may have substantial unmet need but limited capacity to submit detailed regulatory materials. Conversely, a more visible or better-resourced community may be better positioned to nominate candidates even when the evidence base is less mature. FDA's process should account for these differences.

The NHC recommends that FDA evaluate repurposing candidates through a framework that considers unmet medical need, evidence quality, clinical meaningfulness, safety and tolerability, feasibility of use, access implications, and the risk of misinformation or premature uptake. These factors should be considered together rather than sequentially or in isolation. For example, a candidate may have a plausible biological rationale and early clinical signals, but if the proposed use would require intensive monitoring, a formulation that is not practical for the intended population, or a dosing strategy that differs substantially from current labeling, FDA and federal partners may need to consider whether additional study or infrastructure would be necessary before the opportunity can meaningfully benefit patients. Similarly, a candidate with a strong evidence base may still fail to meet patient needs if coverage policies, clinical guidelines, or prescribing information do not reflect the new use in a timely and consistent manner.

A patient-centered framework should also distinguish clinical meaningfulness from statistical or technical measures of effect. Patients with serious, progressive, or life-limiting conditions may value outcomes that are not always captured by traditional endpoints, including preservation of function, reduced fatigue, fewer exacerbations, improved cognition, reduced treatment burden, improved ability to perform daily activities, or delayed need for more invasive interventions.[7,8] The NHC therefore encourages FDA to ensure that patient experience data, caregiver input, and disease-specific expertise inform the evaluation of whether a potential repurposed use meaningfully addresses a need. This does not mean that patient preference should substitute for evidence, but rather that evidence should be assessed in relation to outcomes that matter to the people living with the condition.

Candidates With Sufficient Evidence to Support a New Use

For candidates where sufficient evidence may already exist to support a new use, the NHC recommends that FDA prioritize situations in which a labeling update would provide clear public health value by reducing uncertainty, improving clinical decision-making, and addressing access barriers. This category may include circumstances in which evidence has accumulated over time through published studies, clinical experience, guidelines, registries, or other sources, but no manufacturer has a sufficient commercial incentive to pursue a supplemental application. In such cases, labeling may

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[7] National Health Council, *Patient-Centered Real-World Evidence: Methods. Recommendations from an Evidence-Based Process Consensus* (Washington, DC: National Health Council, May 2021), https://nationalhealthcouncil.org/wp-content/uploads/2021/06/NHC-Patient-Centered-Real-World-Evidence-White-Paper-1.pdf.

[8] Food and Drug Administration, "FDA Patient-Focused Drug Development Guidance Series."

lag behind evidence-based practice, leaving patients and clinicians to navigate inconsistent information and leaving payers to make coverage determinations without the benefit of clear regulatory action.

The NHC supports FDA's continued consideration of approaches such as Project Renewal, which uses publicly available scientific evidence to update labeling for certain older oncology drugs, and encourages FDA to examine whether similar approaches could be adapted to other disease areas where appropriate.[9] Beyond oncology, many disease areas make use of older therapies, generic products, or widely used drugs for which evidence has evolved but labeling remains incomplete or outdated. When FDA has authority to act and the evidence is sufficient, a clear process for updating labeling could help patients, clinicians, and payers by aligning regulatory information more closely with current evidence.

For this category, the NHC encourages FDA to be transparent about the types of evidence that may support a labeling change and how different forms of evidence will be weighed. Depending on the context, relevant evidence may include adequate and well-controlled clinical investigations, confirmatory evidence, systematic reviews, meta-analyses, patient-level data, externally controlled evidence, real-world evidence, mechanistic evidence, clinical guidelines, and long-standing patterns of evidence-supported clinical use.[10,11] The NHC recognizes that not all forms of evidence will be appropriate in all circumstances and that FDA must maintain the statutory standards governing approval of new uses. However, clearer publicly available expectations would help patient organizations, researchers, and clinicians understand when existing evidence may be sufficient and when additional data generation is necessary.

FDA could also strengthen this effort by considering a public process for identifying, triaging, and communicating about candidates in this category. That process could include a standardized nomination template, evidence summary, opportunities for input from patient communities, and transparent communication about process and evidence status, where appropriate. Such a process would also help patient organizations understand how candidates are evaluated, how stakeholders can contribute relevant information, and why a candidate may or may not be appropriate for labeling consideration based on the available evidence. Where FDA determines that a candidate initially identified as potentially supported by sufficient evidence does not meet the threshold for a labeling change, patients and clinicians would benefit from clear

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[9] U.S. Food and Drug Administration, Oncology Center of Excellence, "Project Renewal," last modified January 21, 2026, https://www.fda.gov/about-fda/oncology-center-excellence/project-renewal.

[10] U.S. Food and Drug Administration, *Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Guidance for Industry* (Silver Spring, MD: FDA, August 2023), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug.

[11] U.S. Food and Drug Administration, *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products: Guidance for Industry* (Silver Spring, MD: FDA, September 2022), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-documents-using-real-world-data-and-real-world-evidence-fda-drug-and-biological-products.

communication about what remains unknown and what additional evidence would be needed.

Candidates With Preliminary Clinical Signals

The second category, involving candidates with preliminary clinical signals but insufficient evidence to support a labeling change, may be especially important for patient communities facing serious unmet need. In many disease areas, early clinical observations, case reports, small studies, registries, or specialist experience may suggest potential benefit before a conventional development program exists. Patient organizations may be aware of these signals through community experience, clinician networks, research partnerships, or disease-specific registries. They may also be well positioned to identify whether the benefit, if confirmed, would address outcomes that patients consider meaningful.

At the same time, this category presents the greatest communication challenge. If FDA or federal partners publicly identify a potential use as promising before sufficient evidence exists, patients may reasonably interpret that identification as a stronger endorsement than intended. Clinicians may face pressure to prescribe, researchers may pursue duplicative or underpowered studies, payers may adopt inconsistent coverage policies, and manufacturers may remain uncertain about whether or how to participate. The NHC therefore encourages FDA to pair any public identification of candidates in this category with clear communication regarding the state of the evidence, the limitations of existing data, and the additional information needed to support a labeling change.

FDA and NIH could strengthen this category by developing a more formal evidence-development pathway for promising repurposing candidates. Such a pathway should include early FDA feedback on study design, patient input on meaningful endpoints, consideration of pragmatic or registry-based trials where appropriate, use of natural history data where scientifically justified, and mechanisms for including patients who are often excluded from traditional trials. The pathway should also account for differences in organizational capacity among patient organizations. Patient organizations can help identify unmet need, support recruitment, convene experts, and define meaningful outcomes, but many do not have the resources to design or fund the studies that may be necessary to move a candidate from promising signal to regulatory action. Federal technical assistance, convening, and, where appropriate, support for evidence generation may therefore be useful where the public health value is substantial but traditional development pathways are unlikely to advance the opportunity in a timely manner.

Candidates With Preclinical or Computational Signals

The third category, involving candidates identified through preclinical data, high-throughput screening, in vitro models, artificial intelligence, machine learning, or other computational approaches, should be treated as hypothesis-generating until clinical evidence supports further conclusions. The NHC recognizes that these approaches may help identify non-obvious candidates, reveal plausible mechanisms, and prioritize compounds for additional study. As biomedical data sources expand and analytic tools

become more sophisticated, computational approaches may become increasingly useful in identifying potential repurposing opportunities that would not otherwise be apparent through traditional literature review or clinical observation.

However, the NHC urges FDA to approach this category with particular caution in public communications. Patients with serious unmet needs may be especially vulnerable to overinterpreting early-stage signals, and public identification of a candidate could unintentionally contribute to unsupported use if the limitations of the evidence are not clearly explained The NHC therefore encourages FDA to develop clear standards for how preclinical and computational signals are validated, how uncertainty is communicated, and how such candidates move toward clinical evaluation. These standards should address transparency regarding data sources, model limitations, reproducibility, biological plausibility, relevance to the intended patient population, and the additional steps necessary before clinical benefit can be inferred.

Patient organizations can contribute to this stage by helping prioritize which hypotheses are most relevant to patient needs, but patient engagement should not be used to lend credibility to weak or unsupported signals. FDA and federal partners should ensure that any process involving computational or preclinical repurposing candidates is explicit that such candidates remain investigational. The goal should be to create a responsible translational pathway from signal identification to clinical evaluation, not to blur the distinction between hypothesis generation and evidence-supported care.

Barriers to Repurposing Where Commercial Incentives Are Limited

The NHC encourages FDA to recognize that some repurposing opportunities may face structural evidentiary, regulatory, operational, and financial barriers that make the traditional sponsor-driven pathway difficult to use, even when the public health rationale is strong. In many cases, an approved drug may be generic, off-patent, marketed by multiple manufacturers, or already used in some clinical settings for a condition not reflected in labeling. Although patients, clinicians, researchers, manufacturers, and patient organizations may recognize the potential value of a new use, the evidentiary, regulatory, operational, and financial responsibilities associated with developing that use may not fall clearly to any single entity, particularly where a product is older, generic, off-patent, marketed by multiple manufacturers, or used in a small or difficult-to-study population.[12,13] As a result, repurposing opportunities may fall into a gap between clinical practice, academic research, and regulatory action.

This gap can be especially consequential in disease areas where patients have limited or no approved treatment options. For patients and families, the distinction between a drug that is “known” in clinical practice and a drug that is formally labeled for a new use

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[12] Congressional Budget Office, *Research and Development in the Pharmaceutical Industry* (Washington, DC: CBO, April 2021), https://www.cbo.gov/publication/57126.

[13] Reagan-Udall Foundation for the FDA, *Enhancing Post-Market Evidence Generation for Medical Products* (Washington, DC: Reagan-Udall Foundation, November 2023), https://reaganudall.org/sites/default/files/2023-11/Enhancing%20Post-Market%20Evidence%20Generation%20for%20Medical%20Products%20FINAL_0.pdf.

is not merely technical. Labeling affects clinician confidence, patient understanding, coverage decisions, medical necessity documentation, treatment guidelines, and the ability of the health care system to distinguish evidence-supported care from speculative use. Where labeling lags behind evidence, patients may experience delays, coverage denials, inconsistent access, or uncertainty about whether a treatment option is appropriate for their condition. Conversely, where evidence remains preliminary but public attention is high, patients may be exposed to unrealistic expectations or unsupported claims.

The NHC recommends that FDA and federal partners consider repurposing as a shared public health challenge in circumstances where the traditional sponsor-driven model is unlikely to function effectively. FDA's role is appropriately centered on determining whether the evidence is sufficient to support a new labeled use, but the evidence needed for that determination may not be generated without coordination across federal agencies, patient organizations, academic researchers, clinicians, and, where appropriate, manufacturers. The NHC encourages FDA to clarify how existing authorities may be used when the traditional sponsor-driven supplemental application pathway is not feasible or is unlikely to advance a high-priority public health opportunity in a timely manner.

Different types of commercial disincentives may require different policy or operational responses. For that reason, the NHC recommends that FDA distinguish among them when assessing barriers to repurposing. In some cases, the absence of exclusivity, the presence of multiple manufacturers, or the limited size or complexity of the potential population may make investment in a new indication difficult to sustain through traditional development models. In other cases, a manufacturer may have an approved product but limited interest in pursuing a use that is small, complex, difficult to study, or unlikely to support a commercially viable return. In still other cases, the relevant product may involve supply, formulation, dosage, or manufacturing issues that make repurposing more complicated than the existence of an approved drug might suggest. A transparent repurposing framework should account for these differences and avoid assuming that every potential candidate can be advanced through the same mechanism.

The NHC further recommends that FDA consider whether patient organizations and academic researchers need clearer procedural guidance when they identify a promising repurposing opportunity but cannot themselves serve as a traditional sponsor. Patient organizations are able to identify unmet need, describe patient-relevant outcomes, convene clinicians, support registries, and help recruit for studies, while academic researchers may contribute scientific expertise, evidence synthesis, study design, and analysis of existing clinical or real-world data. However, neither patient organizations nor academic researchers can generally assume the full evidentiary, regulatory, and

operational responsibilities associated with a traditional drug development program.[14,15] FDA and NIH should therefore consider how to provide technical assistance, study-design feedback, evidence-synthesis support, and convening mechanisms that allow these stakeholders to meaningfully contribute without shifting inappropriate burdens onto them.

Barriers for Patients and Clinicians When Approved Drugs Are Used for Unapproved Uses

The RFI's questions regarding barriers to using FDA-approved drugs for unapproved uses are particularly important from the patient perspective. In many disease areas, clinicians may consider an off-label use based on emerging evidence, clinical guidelines, compendia, specialist experience, or individualized patient need. Such use may be medically appropriate, but the practical experience for patients can vary substantially depending on payer policy, clinician familiarity, documentation requirements, pharmacy benefit design, and the extent to which the relevant evidence has been incorporated into labeling, guidelines, or coverage criteria. The NHC encourages FDA to examine these barriers not as a substitute for labeling updates where evidence is sufficient, but as part of understanding why repurposing matters to patients in the first place.

Patients may encounter coverage uncertainty or denials when a drug is prescribed for a use not reflected in FDA-approved labeling, particularly where the supporting evidence has not yet been consistently reflected in compendia, guidelines, or payer coverage criteria.[16,17] These denials can be especially difficult for patients with serious, rare, or complex conditions, where the number of approved therapies may be limited and clinicians may reasonably look to evidence-supported uses of existing products. Patients may also face prior authorization requirements that require extensive documentation, repeated resubmissions, appeals, or peer-to-peer reviews. These processes can delay treatment, increase administrative burden on clinicians, and create inequities between patients whose providers have the time and infrastructure to navigate coverage requirements and those whose providers do not.

The NHC also encourages FDA and federal partners to examine the interaction between labeling status, compendia recognition, clinical guidelines, and payer policy. A

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[14] National Academies of Sciences, Engineering, and Medicine, *Realizing the Promise of Real-World Evidence to Accelerate Drug Development and Evaluation: Proceedings of a Workshop* (Washington, DC: National Academies Press, 2026), https://www.nationalacademies.org/projects/HMD-HSP-23-08/publication/27968.

[15] EveryLife Foundation for Rare Diseases, *Guide to Patient Involvement in Rare Disease Product Development* (Washington, DC: EveryLife Foundation, January 2022), https://everylifefoundation.org/wp-content/uploads/2022/01/Guide-to-Patient-Involvement-FINAL-COMPLETE-GUIDE-Rev.pdf.

[16] Barbieri et al., "Evaluation of Clinical Compendia," 315–320.

[17] Abbi Coursolle, *More Transparency Needed to Ensure Medicaid Beneficiaries Have Access to Necessary Off-Label Prescription Drugs* (Washington, DC: National Health Law Program, April 2022), https://healthlaw.org/wp-content/uploads/2022/04/2022-04-07-Off-Label-Paper-Final.pdf.

drug may be supported by some clinical evidence but not yet reflected in labeling. It may be included in some guidelines but not others. It may be recognized in a compendium for one use but not another. These misalignments can produce inconsistent access and confusion for patients, clinicians, and payers. For patients, the result may be that access depends less on the strength of the evidence or the appropriateness of the therapy than on the timing and alignment of multiple systems that do not always move together.

Patients may also struggle to understand the difference between approved use, off-label use, evidence-supported use, investigational use, and unsupported use. These distinctions matter because they affect expectations, risk tolerance, informed consent, coverage, and trust. A patient who is told that a drug is "used for" a condition may not understand whether that use is FDA-approved, commonly accepted in practice, supported by limited evidence, or still speculative. FDA can help address this problem by communicating clearly when evidence is sufficient to support labeling, when evidence is promising but incomplete, and when additional study is needed before clinical benefit can be inferred.

The NHC does not suggest that FDA determine payer coverage or interfere with appropriate clinical discretion. However, FDA's actions can reduce uncertainty by clarifying the state of evidence and updating labeling when appropriate. FDA and CMS should also consider whether there are opportunities to better understand how coverage denials, prior authorization requirements, appeals, exceptions processes, and patient cost-sharing affect access to repurposed or evidence-supported off-label therapies. This information would help federal agencies and stakeholders identify where regulatory clarity, evidence development, or coverage policy alignment may be needed to ensure that patients can access medically appropriate care.

Data Collection and Real-World Evidence

The NHC supports FDA's interest in understanding how approved drugs are being used by the patient community and how real-world data may inform repurposing efforts. Real-world data may help identify patterns of off-label use, patient populations receiving a therapy, potential safety concerns, dosing practices, treatment duration, comparative outcomes, and access barriers. These data may be particularly useful in areas where randomized trials are difficult to conduct, diseases are rare or heterogeneous, or existing evidence is distributed across clinical practice rather than concentrated in a traditional development program. However, real-world data must be fit for purpose, interpreted carefully, and supplemented by patient and clinical context.

Claims data may help federal agencies understand prescribing patterns, utilization, coverage denials, appeals, treatment switching, and cost-sharing; however, claims data often lack clinical detail, disease severity, patient-reported outcomes, reasons for prescribing, and information about whether a treatment produced meaningful benefit.[18,19] Electronic health records (EHR) may provide richer clinical information, but

[18] U.S. Food and Drug Administration, *Considerations for the Use of Real-World Data*.

EHR data can vary in quality, completeness, interoperability, and representativeness. Registries and natural history studies may provide valuable longitudinal information, particularly in rare diseases and chronic conditions, but they may require sustained funding, governance, and standardization. Patient-reported data can capture symptoms, function, quality of life, treatment burden, and tolerability, but these data must be collected in ways that minimize burden and support meaningful interpretation.

The NHC encourages FDA to develop principles for using real-world data in drug repurposing that address data quality, relevance, representativeness, transparency, patient privacy, bias, missing data, and outcome validity. These principles should also address when real-world data may be sufficient to contribute to regulatory decision-making and when such data should instead be treated as hypothesis-generating or supportive. Clear expectations would help patient organizations, researchers, clinicians, and data holders understand how to design studies and data systems that are more likely to inform FDA's evaluation.

Patient organizations should be involved in determining which outcomes are meaningful and how data collection can be designed in ways that reflect the lived experience of patients and caregivers. In many disease areas, traditional clinical measures may not fully capture the outcomes that matter most to patients, such as fatigue, cognition, pain, mobility, independence, daily functioning, caregiver burden, or ability to participate in work, school, family, or community life. Patient organizations can help ensure that real-world evidence generation does not focus exclusively on measures that are easy to capture in existing systems but not particularly meaningful to the people living with the condition.

The NHC also recommends that FDA and federal partners consider how to ensure that patient communities receive value from data collection. Patients and patient organizations are often asked to contribute data, participate in registries, support recruitment, or explain the burden of disease, yet the results of these efforts may not always be communicated back to the community in a timely or usable way. A patient-centered repurposing framework should include expectations for transparency, feedback, plain-language summaries, and responsible dissemination of findings. Patients who contribute data should understand how the data will be used, what questions the data may help answer, and what limitations remain.

Role of Patient Organizations

Patient organizations must be central partners in any federal repurposing framework. They are uniquely positioned to identify unmet needs, describe the real-world burden of disease, explain which outcomes are meaningful, identify practical barriers to treatment, and convene patients, caregivers, clinicians, researchers, and other stakeholders. In some disease areas, patient organizations may also support registries, natural history studies, research networks, endpoint development, patient preference studies, and community education. These capabilities can make patient organizations essential partners in identifying and evaluating repurposing opportunities.

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[19] National Health Council, *Patient-Centered Real-World Evidence*.

At the same time, the NHC encourages FDA to recognize the significant variation in capacity between patient organizations. Some patient organizations have substantial scientific, regulatory, and data infrastructure, while others operate with limited staff and resources. Smaller organizations may represent conditions with profound unmet need but lack the ability to prepare detailed evidence submissions, manage registries, or convene technical expert panels. A repurposing framework that depends heavily on the sophistication or resources of individual organizations could inadvertently advantage better-resourced communities and overlook patients with equally serious needs.

The NHC encourages FDA to create practical engagement mechanisms that allow patient organizations to contribute within their capacity. FDA could develop a plain-language guide explaining how the repurposing process works, what types of input are most useful, how patient experience data may inform prioritization, and what level of evidence is needed at different stages. FDA could also provide a standardized nomination template that allows patient organizations to describe unmet need, current treatment limitations, patient-relevant outcomes, known or suspected use of approved drugs, and barriers to evidence generation without requiring them to produce a full regulatory dossier.

FDA could further strengthen patient engagement through public listening sessions, disease-area workshops, technical assistance webinars, and opportunities for patient organizations to comment on candidate prioritization and evidence gaps. These mechanisms would help ensure that patient input informs the process early, rather than being solicited only after FDA or federal partners have already selected candidates. Early engagement is important because patient organizations can help identify whether a potential repurposing opportunity would address a meaningful problem for patients, whether the proposed outcomes reflect patient priorities, and whether the therapy would be feasible in real-world care.

The NHC also recommends that FDA consider how to manage conflicts of interest and preserve trust in a repurposing process that may involve patient organizations, manufacturers, researchers, clinicians, and payers. Patient organizations often collaborate with a range of stakeholders, including industry, because such collaboration can support research, education, and access. The NHC encourages FDA to recognize that such collaboration can be appropriate and constructive when accompanied by transparency, safeguards, and scientific independence. A clear process for disclosing relevant relationships, explaining how input is weighed, and maintaining scientific independence would help protect the credibility of the repurposing initiative.

Coverage and Access Considerations

The NHC emphasizes that a labeling change, while important, does not automatically ensure patient access. For patients, the practical value of repurposing depends on whether the therapy can be prescribed, covered, obtained, and used without unnecessary delay or cost. Even after evidence supports a new use, patients may continue to face uncertainty if labeling, compendia, clinical guidelines, payer coverage criteria, prior authorization processes, and pharmacy benefit systems do not evolve promptly and consistently. These issues are particularly important for patients with

chronic, rare, complex, or progressive conditions, for whom delays in treatment can have significant consequences.

The NHC encourages FDA to work with CMS and other federal partners to better understand how coverage and access barriers affect repurposed therapies. While FDA does not make coverage decisions, FDA's determinations can influence payer policy by clarifying whether evidence is sufficient to support a labeled use. CMS, in turn, may be able to identify how Medicare and Medicaid beneficiaries experience access barriers related to labeling status, compendia recognition, prior authorization, medical necessity documentation, appeals, and cost-sharing. Coordinated federal attention to these issues would help ensure that repurposing initiatives do not stop at the point of regulatory action but instead translate into meaningful patient benefit.

The NHC recommends that FDA and CMS examine how labeling updates for repurposed uses are reflected across coverage, compendia, guideline, and clinical decision-making systems over time. In some cases, a labeling change may be quickly incorporated into clinical practice and payer policy. In other cases, delays or misalignment may persist, leaving patients and clinicians uncertain about coverage. FDA and CMS should also consider whether certain populations are more likely to experience access barriers, including patients with rare diseases, multiple chronic conditions, receiving care from smaller or less-resourced clinical practices, and patients whose conditions are not well represented in traditional clinical guidelines.

The NHC also encourages federal partners to consider the administrative burden associated with accessing repurposed or evidence-supported therapies. Although utilization management tools may serve important functions when appropriately designed and implemented, prior authorization, step therapy, repeated documentation requests, and appeals can create substantial burdens for patients, caregivers, and clinicians when they are not timely, transparent, clinically appropriate, or aligned with the evidence supporting the requested therapy.[20,21] These processes may be particularly harmful when they delay treatment for serious or progressive conditions or when they require patients to fail therapies that are not clinically appropriate for their circumstances. A patient-centered repurposing framework should therefore consider not only whether a therapy is covered in theory, but whether patients can access it in practice without unnecessary delay or administrative complexity.

Finally, the NHC asks that FDA and CMS consider how patient cost-sharing may affect access to repurposed therapies. Some repurposed drugs may be relatively inexpensive, but others may involve higher costs depending on formulation, dosage, route of administration, site of care, pharmacy benefit design, or supply factors. Even modest

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[20] National Health Council, *Exploring the Burden of Prior Authorization on Patients with Chronic Disease* (Washington, DC: National Health Council, November 2023), https://nationalhealthcouncil.org/wp-content/uploads/2023/11/NHC-Report-Exploring-the-Burden-of-Prior-Authorization-on-Patients-with-Chronic-Disease.pdf.

[21] Karen Pollitz and Jeannie Fuglesten Biniek, "Final Prior Authorization Rules Look to Streamline the Process, but Issues Remain," KFF, February 27, 2024, https://www.kff.org/private-insurance/final-prior-authorization-rules-look-to-streamline-the-process-but-issues-remain/.

cost-sharing can be a barrier for some patients, especially those managing multiple chronic conditions or recurring treatment expenses. Federal coordination should therefore include attention to affordability and out-of-pocket exposure, particularly where repurposing is intended to address serious unmet need.

Maintaining Scientific Standards and Patient Trust

The NHC supports FDA's exploration of drug repurposing, but the agency should make clear that repurposing is not a lower-evidence pathway or a substitute for rigorous evaluation. Patients with serious and chronic conditions often face difficult choices under conditions of uncertainty, and many are willing to accept some degree of risk when treatment options are limited. However, patients also rely on FDA to distinguish therapies supported by adequate evidence from therapies supported only by anecdote, theory, or early signals. Maintaining that distinction is essential to preserving patient trust.

A patient-centered repurposing framework should therefore delineate between uses that are supported by sufficient evidence for labeling, uses that have promising clinical signals but require additional study, uses that are supported only by preclinical or computational hypotheses, and uses that are unsupported or potentially unsafe. These distinctions should be reflected not only in internal FDA review but also in public communications. When FDA identifies a repurposing candidate, patients and clinicians should be able to understand whether the candidate is ready for labeling consideration, needs further clinical evidence, or remains at a much earlier stage of investigation.

The NHC also encourages FDA to apply benefit-risk assessment in a manner that accounts for the proposed use, the intended patient population, disease severity, available alternatives, dosage, duration, and clinical context. A drug's known safety profile in one population or indication may not translate directly to another use. Patients with organ impairment, advanced disease, pregnancy, older age, pediatric disease, multiple chronic conditions, or concomitant therapies may face different risks. Conversely, patients with serious, progressive, or life-limiting conditions may reasonably value potential benefits differently than patients with conditions for which multiple effective options already exist. Patient input should inform FDA's understanding of benefit and risk, while FDA's scientific judgment should continue to determine whether the evidence is sufficient.

FDA should also consider how to guard against misinformation or premature uptake. Public interest in repurposing can be high, particularly when patients lack approved options or when early signals are amplified through media, social media, or informal clinical networks. FDA communications about candidates that are promising but not yet proven should be carefully framed to avoid language that could be interpreted as endorsing clinical use before adequate evidence exists. Clear, plain-language communication about what is known, what remains uncertain, and what evidence is still needed would help patients make informed decisions and help clinicians counsel patients responsibly.

Transparency and Public Communication

Transparency will be critical to the credibility and usefulness of FDA's repurposing initiative. The NHC encourages FDA to publish clear criteria for prioritizing disease areas and candidates, explain how evidence will be evaluated, identify opportunities for patient and clinician input, and communicate the status of nominated or selected candidates. Without transparency, patient communities may not understand why certain candidates advance while others do not, and stakeholders may be less able to align evidence-generation efforts with FDA's needs.

A more structured and transparent process, such as a standardized nomination mechanism or evidence-status framework, could help stakeholders understand how candidates are identified, evaluated, and communicated. This process should not disclose confidential information inappropriately or create expectations that every nomination will receive extensive FDA review. However, a transparent process could help stakeholders understand whether a candidate has been received, whether it appears to fall within a category that may warrant further review, whether additional evidence is needed, and whether federal partners or external researchers may have a role in addressing evidence gaps.

The NHC also recommends that FDA develop plain-language materials for patients and caregivers. These materials should explain what drug repurposing is, how it differs from off-label use, what a labeling change means, what it means when evidence is promising but insufficient, and how patients can interpret information about repurposing candidates. Such materials would be especially useful in disease areas where patients are actively seeking options and may encounter information of varying quality. Clear communication can help prevent misunderstandings and support informed discussions between patients and clinicians.

In addition, the NHC encourages FDA to consider how to communicate when it determines that evidence is not sufficient to support a new use. Clear explanations of these decisions may be difficult, but they are important for patient trust. If a therapy is widely discussed in a patient community but FDA concludes that evidence is inadequate, patients deserve a clear explanation of the agency's reasoning, the limitations of the evidence, and what additional information would be needed. Such transparency would help distinguish FDA's scientific assessment from a lack of concern for the affected community and may help guide future research.

Federal Coordination

The NHC urges FDA to explore, in coordination with NIH, CMS, the Agency for Healthcare Research and Quality, and other federal partners, how existing federal roles and authorities could better support appropriate drug repurposing efforts. FDA is central to determining whether evidence supports labeling, but FDA alone cannot resolve the barriers that prevent repurposing opportunities from reaching patients. NIH may be needed to support evidence generation, trial networks, natural history studies, translational research, and endpoint development. CMS may be needed to understand coverage, prior authorization, appeals, and beneficiary access barriers. AHRQ may be able to support evidence synthesis, comparative effectiveness research, and

dissemination of findings. Other federal partners may have disease-specific data, public health expertise, or implementation responsibilities.

A coordinated federal strategy should begin with shared criteria for identifying high-priority repurposing opportunities. These criteria should include unmet medical need, seriousness of the condition, adequacy of existing therapies, patient and caregiver burden, strength of evidence, feasibility of additional evidence generation, and potential to improve patient access or clinical decision-making. Federal partners should also consider whether the absence of commercial incentive is a central barrier and whether federal action could reasonably help move the opportunity forward.

The NHC recommends that FDA and NIH consider creating a pathway for high-priority candidates that require additional evidence. This pathway could include early regulatory feedback, technical assistance on study design, use of patient-centered endpoints, support for pragmatic or registry-based studies where appropriate, and mechanisms for engaging patient organizations and clinical experts. Such a pathway would be especially valuable where evidence is promising but fragmented and no traditional sponsor is likely to pursue a supplemental application without federal coordination.

The NHC also encourages FDA and CMS to examine how regulatory and coverage processes interact after evidence supports a new use. While FDA and CMS have separate responsibilities, patients experience these systems as connected. A labeling update may not improve access if coverage criteria are slow to change, if prior authorization processes remain unclear, or if patients face substantial cost-sharing.[22,23,24] Similarly, coverage policies may be difficult to develop or apply consistently when evidence is promising but not yet reflected in labeling. FDA and CMS should therefore identify opportunities to improve communication, share evidence summaries where appropriate, and better understand how access barriers affect patients after repurposing decisions are made.

Coordination should not compromise FDA's scientific independence or CMS's coverage responsibilities. Rather, coordination should ensure that promising repurposing opportunities do not stall because no single actor has responsibility for evidence generation, labeling, dissemination, and access. A federal framework that preserves agency roles while improving alignment would better serve patients, clinicians, and the broader health care system.

Taken together, these steps would help FDA use this RFI to clarify how repurposing opportunities can be identified, evaluated, communicated, and connected to patient needs without weakening evidentiary standards.

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[22] National Health Council, *Exploring the Burden of Prior Authorization*.

[23] Barbieri et al., "Evaluation of Clinical Compendia."

[24] Lee et al., "Updated Resource."

Conclusion

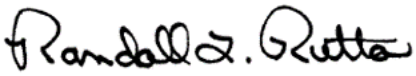
The NHC appreciates FDA's attention to drug repurposing as a potential strategy to address unmet medical needs. Repurposing may offer meaningful benefits where an approved drug has a known safety profile, accumulated clinical experience, and evidence suggesting a new use, particularly where limited commercial incentives have prevented the traditional supplemental approval pathway from operating effectively. For patients, however, the promise of repurposing depends on more than identifying candidate drugs. It depends on rigorous evidence, patient-centered prioritization, clear labeling, transparent communication, attention to coverage and access implications, and coordinated federal action.

The NHC encourages FDA to build a repurposing framework that is scientifically rigorous, patient-centered, transparent, and connected to real-world access. Such a framework should engage patient organizations from the outset, distinguish clearly among levels of evidence, support evidence generation where needed, and coordinate with federal partners to ensure that regulatory action translates into meaningful benefit for patients. The NHC emphasizes that patient organizations are essential partners for FDA in identifying unmet need and meaningful outcomes, while also ensuring that the process does not place unrealistic technical or operational burdens on organizations with limited resources.

Please do not hesitate to contact Kimberly Beer, Senior Vice President, Policy & External Affairs, at kbeer@nhcouncil.org, or Shion Chang, Assistant Vice President, Policy & Regulatory Affairs, at schang@nhcouncil.org, if you or your staff would like to discuss these comments in greater detail.

The NHC appreciates the opportunity to provide these comments and welcomes continued engagement with FDA on this important issue.

Sincerely,



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