

THE ALLIANCE FOR
LONGEVITY INITIATIVES

The Multi-Disease Therapeutic Designation

A Coordination Pathway for Integrated Risk Reduction Trials in Chronic Disease

For inclusion in the PDUFA VIII Reauthorization

Executive Summary

This whitepaper proposes the Multi-Disease Therapeutic Designation (MDTD), a new regulatory framework designed to modernize how the FDA evaluates therapies targeting the shared biological drivers of chronic disease. While existing expedited designations and pathways such as Breakthrough Therapy, Regenerative Medicine Advanced Therapy (RMAT), and Accelerated Approval have transformed drug development, they remain rooted in a 'one drug, one disease' paradigm. This legacy architecture is optimized for reactive disease management: treating patients only after they cross a formal diagnostic threshold. MDTD establishes a dedicated regulatory home for integrated risk-reduction trials—studies designed not merely to manage existing symptoms, but to demonstrate that a single intervention can reduce the risk of onset or progression across multiple chronic conditions simultaneously. In doing so, MDTD serves as a critical administrative vehicle for advancing the FDA's broader clinical trial modernization agenda. It provides the structured pathway required to operationalize master protocols, facilitate early cross-center scientific engagement, and establish dedicated expedited tracks for complex, multi-indication programs. To maintain regulatory rigor, MDTD is a narrow, mechanism-based framework; it explicitly does not create a diffuse "healthspan" or "longevity" indication. Instead, eligibility is strictly limited to programs that demonstrate clinical proof-of-concept in an initial serious chronic condition, paired with a qualifying mechanism of action and robust nonclinical efficacy that substantiate its potential across distinct disease classes. The upcoming PDUFA VIII reauthorization represents the ideal legislative vehicle to align FDA oversight with the convergent biology of modern medicine.

1. The Regulatory Mismatch

These complex, multi-disease conditions are particularly prevalent in older adult populations, where nearly 45% of Medicare beneficiaries live with four or more conditions simultaneously.

1.1 Convergent Mechanistic Drivers of Chronic Disease

For most of the twentieth century, biomedical science treated chronic diseases as discrete entities: cardiovascular disease was a problem of the heart and vasculature, type 2 diabetes a problem of metabolism, Alzheimer's a problem of the brain, cancer a problem of cell-cycle regulation. The institutions of biomedical research — including the FDA's review divisions were organized accordingly.

Over the past two decades, research into mechanistic pathophysiology has demonstrated that this organizational logic does not match the underlying biology. The major chronic diseases share a common set of mechanistic drivers — the so-called hallmarks of multimorbidity: genomic

instability, telomere attrition, epigenetic alterations, loss of proteostasis, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, dysregulated nutrient sensing, altered intercellular communication, chronic inflammation, and additional hallmarks added in more recent reviews.

These hallmarks interact and amplify one another. Mitochondrial dysfunction generates reactive oxygen species that damage DNA, accelerating genomic instability. Genomic instability triggers cellular senescence, which propagates chronic low-grade inflammation through pro-inflammatory cytokines, which in turn drives vascular damage, insulin resistance, and neurodegeneration. The clinical diseases differ; the upstream biology is convergent.

This understanding has produced a growing class of investigational therapies that target hallmark biology rather than disease-specific pathology. Senolytic drugs designed to clear senescent cells. mTOR inhibitors that modulate nutrient sensing. NAD+ precursors aimed at mitochondrial function. Metformin, repurposed in the Targeting Metformin (TAME) trial as the first multi-disease risk reduction trial designed around shared biology. Each of these candidates is being evaluated against multiple chronic disease endpoints simultaneously.

The clinical reality of these shared biological drivers is that they are actionable before end-stage disease appears. While current drug development focuses on "downstream" outcomes—treating cardiovascular disease after a heart attack or neurodegeneration after cognitive impairment, the convergent biology of chronic disease offers a unique window for "upstream" interception. MDTD identifies the regulatory infrastructure needed to capitalize on this window, shifting the focus from late-stage disease management to early-stage risk reduction.

1.2 Case Studies in Regulatory Friction: Evidence for Modernization

The FDA's review apparatus is organized by clinical indication—cardiology, oncology, neurology—creating a rigid, siloed structure. This "one-division, one-disease" framework forces sponsors seeking multi-indication claims to navigate redundant, disconnected development programs.

The Targeting Aging with Metformin (TAME) trial offers a masterclass in trial design for the risk reduction of chronic multimorbidity. Its multi-site design and rigorous, prospectively-defined composite endpoint for incident chronic disease—spanning myocardial infarction, stroke, cancer, and dementia—set a gold standard for how risk reduction trials should be structured. The hurdle is not scientific; it is that our current architecture forces sponsors to engage in bespoke, siloed negotiations rather than utilizing a predictable, scalable pathway.

We see this friction commercially with SGLT2 inhibitors and GLP-1 receptor agonists. Despite their profound capacity to impact shared metabolic drivers, sponsors are forced to pursue these indications sequentially, not in parallel. Each expansion requires massive, multi-year pivotal trial programs and separate, siloed interactions with different review divisions. This serial regulatory

approach is a legacy artifact of an architecture designed for an era where single-mechanism drugs were rare.

Crucially, the regulatory infrastructure to manage these therapeutics is already feasible, as proven by the FDA's Center for Veterinary Medicine (CVM). Loyal, a clinical-stage veterinary company, is currently utilizing the CVM's expanded conditional approval pathway for its chronic condition drug. If a regulatory pathway for multi-disease risk reduction is already operational for veterinary medicine, the institutional mechanism to regulate this class of science is inherently feasible for human use. MDTD simply adapts this proven logic to the human regulatory context, replacing duplicative, bespoke interactions with a standardized, cross-divisional framework.

2. The Proposal: Alignment with FDA's Efforts to Modernize Clinical Trials

To qualify for MDTD, a sponsor must prospectively specify a development program where the primary objective is the risk reduction of incident disease events or the reduction of risk across two or more conditions from a defined, statutory list of serious chronic diseases (e.g., composite incidence of MACE plus renal events). This designation is restricted to risk-reduction claims; it does not apply to the treatment of established, symptomatic multi-organ failure. This proposal positions the Multi-Disease Therapeutic Designation (MDTD) not as an isolated regulatory add-on, but as a critical infrastructure component for the FDA's ongoing clinical trial modernization efforts. MDTD serves as the administrative mechanism to execute three key objectives for regulatory efficiency: The MDTD framework utilizes existing FDA consultation mechanisms and provides a statutory mandate for a designated cross-center coordination point, ensuring sponsors have a predictable, streamlined channel of communication without imposing new organizational structures or interfering with FDA's internal governance.

2.1 Establishing Chronic Disease-Expert Centers as Qualified Research Institutions (QRIs)

The FDA's ongoing modernization efforts for clinical trials emphasize the role of Qualified Research Institutions (QRIs) in providing pre-submission, FDA-aligned guidance to reduce IND uncertainty. We propose that centers of excellence in chronic disease biology be formally designated as the primary network of QRIs for the MDTD program. This designation grants sponsors a "pre-clearance" path to discuss multi-morbidity endpoints early, directly fulfilling the FDA's commitment to early scientific engagement to reduce IND uncertainty and clarify evidentiary requirements for complex developmental programs.

2.2 Operationalizing Master Protocols for Multi-Morbidity

The FDA explicitly encourages the use of Master Protocols to evaluate multiple conditions simultaneously. MDTD provides the regulatory infrastructure to operationalize this for multimorbidity. An MDTD program is defined by its use of a single, integrated "Master Protocol" that tracks multiple conditions, such as cardiovascular disease and type 2 diabetes

within one statistical framework. This aligns perfectly with the FDA's goal to standardize Master Protocols and eliminate duplicative, siloed trial infrastructure.

2.3 Prioritizing Expedited INDs for Novel Multi-Disease Modalities

To foster clinical efficiency and reduce development redundancy, we propose that MDTD programs utilizing an integrated Master Protocol be prioritized for the FDA's ongoing "Expedited IND" pilot. Developing an integrated trial capable of generating substantial evidence across multiple chronic conditions is a task of significant regulatory complexity. Prioritizing these programs for expedited review acknowledges the administrative investment made by sponsors to conduct high-efficiency, multi-disease risk reduction trials. This prioritization is consistent with the agency's broader goal to modernize clinical development by incentivizing sponsors to consolidate redundant clinical programs into single, integrated, and statistically rigorous development plans.

2.4 Integrating Emerging Measurement Framework: ARPA-H PROSPR Program

The regulatory viability of MDTD is bolstered by ongoing federal and global efforts to standardize functional measurement. Specifically, the ARPA-H PROACTIVE Solutions for Prolonging Resilience (PROSPR) program is currently developing "Intrinsic Capacity" (IC) scores—composite metrics of an individual's physical and mental abilities that serve as predictive surrogates for long-term health outcomes. MDTD provides the regulatory "landing zone" for these innovations. By allowing sponsors to utilize ARPA-H-validated IC scores as prospective surrogate endpoints within an MDTD Master Protocol, the FDA can replace traditional, decades-long outcomes trials with more efficient, functional measures of health outcomes. Aligning the MDTD pathway with these initiatives ensures that the FDA's regulatory framework evolves in lockstep with the cutting-edge science emerging from ARPA-H and the broader chronic disease ecosystem.

2.5 Integrated Risk Reduction Trial Design

An MDTD-eligible program typically employs a 5–7 year seamless, multistage, randomized trial in adults with multimorbidity, powered for composite endpoints across cardiovascular, renal, and cognitive outcomes, utilizing time-to-first-event and total-event analyses. Unlike today's process—which requires separate pre-INDs, separate primary endpoints for each review division, and potentially duplicative trial programs—an MDTD program functions under one integrated protocol and a shared Statistical Analysis Plan (SAP) negotiated with a cross-divisional team.

3. The Economic and Strategic Case

3.1 Federal Fiscal Exposure

The current healthcare model is a "sick-care" system optimized for late-stage decline. True fiscal sustainability requires a transition toward proactive, risk reduction. Chronic conditions drive 90

percent of the nation's $4.9 trillion in annual healthcare spending, with nearly half of Medicare beneficiaries living with four or more conditions simultaneously. MDTD provides the regulatory foundation for therapies that reduce the risk of onset of multiple conditions, shifting the system from reactive management to cost-avoiding risk reduction.

3.2 Administrative and Trial Efficiency

The current regulatory architecture imposes a hidden "administrative tax" on multi-indication development. MDTD eliminates this redundancy. By establishing a single, prospective protocol and shared Statistical Analysis Plan (SAP), sponsors can generate data in parallel rather than sequentially. This reduces trial cycle time and administrative overhead, ensuring that capital is directed toward clinical development rather than redundant regulatory filings.

3.3 Competitiveness

Regulatory clarity is a principal variable determining where the next generation of chronic disease drug development is anchored. Other nations are aggressively investing in chronic disease research infrastructure. MDTD is a low-cost, high-leverage tool to ensure the U.S. remains the anchor for this category.

4. Precedent and Legislative Vehicle

4.1 Congress Has Created Pathways Like This Before

The Multi-Disease Therapeutic Designation is not a novel category of legislation. Congress has repeatedly used must-pass legislative vehicles to create or expand FDA expedited designations and pathways when existing structures did not fit an emerging therapeutic category.

The Breakthrough Therapy Designation itself was established by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA), which was the PDUFA V reauthorization. The designation was added through Title IX of that legislation, with statutory criteria worked out in the months preceding enactment by the committees of jurisdiction. There was no new appropriation. There was no new office. The provision became one of the most consequential drug-development reforms of the past three decades.

The Regenerative Medicine Advanced Therapy designation was established by the 21st Century Cures Act of 2016. RMAT was a separate procedural reform: it created a new designation for a category of therapies — cell and gene therapies, tissue engineering products — that had not been contemplated when Breakthrough was originally drafted. The Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD) was also established by the 21st Century Cures Act as a separate pathway for drugs addressing serious or life-threatening infections in limited populations with unmet needs.

RMAT and LPAD provide the closer statutory analogy for MDTD: Congress identified a gap in the existing architecture and added a targeted provision. The MDTD provision is the next iteration of that pattern for therapies targeting shared biology across multiple serious chronic diseases.

5. Conclusion

The chronic diseases represent the greatest fiscal and clinical challenge to the American healthcare system. While our biomedical research has moved toward an understanding of the shared, mechanistic drivers of these conditions, our regulatory apparatus remains fragmented, forcing sponsors to develop therapies for complex, multi-organ diseases one indication at a time.

This fragmentation is not a failure of the FDA's mission; it is a structural misalignment between modern biology and legacy administrative architecture. The Multi-Disease Therapeutic Designation (MDTD) is a targeted, procedural correction. It creates no new appropriations, requires no new offices, and lowers no safety or efficacy standards. Instead, it provides the essential coordination mechanism for therapies designed to reduce the risk of onset of multiple serious conditions simultaneously.

By aligning FDA's expedited pathway architecture with the convergent biology of chronic disease, this provision serves the FDA's clinical trial modernization efforts, increases the efficiency of drug development, and offers a direct path to reduce the long-term fiscal burden of multi-morbidity on Medicare and Medicaid. It is a proven, precedent-based strategy, consistent with the procedural reforms Congress has successfully championed in every PDUFA cycle for the past two decades.

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The Alliance for Longevity Initiatives respectfully urges the House Energy and Commerce Committee, the Senate HELP Committee, and the bipartisan Congressional Longevity Science Caucus to include the Multi-Disease Therapeutic Designation in the PDUFA VIII reauthorization package.

Proposed Legislative Language

SEC. [XXX]. MULTI-DISEASE THERAPEUTIC DESIGNATION (MDTD) ACTIONS AND INTEGRATION.

Section 506(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(i)) is amended by adding at the end the following new subsections:

(i) MULTI-DISEASE THERAPEUTIC DESIGNATION (MDTD).

(1) DESIGNATION. The Secretary shall designate a drug as a multi-disease therapeutic if —

(A) the drug is supported by preliminary clinical evidence demonstrating safety, target engagement, or therapeutic efficacy in at least one serious chronic disease; and

(B) nonclinical evidence and biological characterization demonstrate that the drug's mechanism of action modulates pathophysiological pathways common to one or more additional serious chronic conditions belonging to distinct disease categories.

(2) ACTIONS. Such a drug shall be eligible for intensive guidance on efficient development beginning as early as Phase 1, engagement of senior agency officials, and rolling review of the application.

(3) CROSS-DIVISIONAL REVIEW. Upon designation, the Secretary shall convene a cross-divisional review team, with a designated lead division, to coordinate pre-IND, end-of-Phase-2, and pre-NDA interactions across each indication addressed.

(4) EVIDENTIARY CRITERIA.

(A) CLINICAL PROOF-OF-CONCEPT. The requirement under paragraph (1)(A) may be satisfied by clinical trial data establishing efficacy, validated surrogate endpoint modulation, or intermediate clinical benefit within a primary anchor disease.

(B) MECHANISTIC AND NONCLINICAL EXPANSION. The requirement under paragraph (1)(B) may be satisfied by robust *in vivo* or translational disease models, functional assays, or biomarker evidence demonstrating that the target biological pathway is conserved and clinically relevant across the additional indicated disease categories.

(5) DEFINITION. "Serious chronic disease" includes cardiovascular disease, type 2 diabetes, Alzheimer's disease and related dementias, chronic kidney disease, idiopathic pulmonary fibrosis, osteoarthritis, sarcopenia, and age-related macular degeneration, as further specified in guidance.

(6) GUIDANCE. Not later than 18 months after enactment, the Secretary shall issue draft guidance on trial designs and endpoints for multi-disease prevention claims.

(7) QUALIFIED RESEARCH INSTITUTIONS (QRI) COORDINATION. The Secretary shall designate centers of excellence in chronic disease biology as Qualified Research

Institutions (QRIs) for MDTD-designated programs. The Secretary shall facilitate pre-submission guidance and regulatory consultation between sponsors and designated QRIs to reduce IND uncertainty and clarify evidentiary requirements for complex multi-morbidity development programs.

(8) MASTER PROTOCOLS. The Secretary shall establish procedures to operationalize Master Protocols for MDTD-designated programs. The Secretary shall permit and encourage the use of a single, integrated protocol that tracks multiple conditions within a unified statistical framework, ensuring consistent regulatory expectations across review divisions.

(9) EXPEDITED IND PRIORITIZATION. The Secretary shall prioritize MDTD-designated programs utilizing an integrated Master Protocol for participation in ongoing expedited IND pilots. Such prioritization shall be based on the complexity of the development program and the administrative investment by the sponsor in consolidating redundant clinical programs into single, integrated, and statistically rigorous plans.

(10) INTEGRATION OF EMERGING MEASUREMENT FRAMEWORKS. The Secretary shall issue guidance on the use of standardized functional measurement frameworks, including but not limited to ARPA-H validated "Intrinsic Capacity" (IC) scores, as prospective surrogate endpoints within an MDTD Master Protocol. The Secretary shall ensure that such frameworks are evaluated for their utility as predictive surrogates for long-term health outcomes.

(11) INTEGRATED RISK REDUCTION TRIAL DESIGN. The Secretary shall facilitate the development of integrated risk reduction trials. For MDTD-designated programs, the Secretary shall provide for the negotiation of a shared Statistical Analysis Plan (SAP) with a cross-divisional team, allowing for the concurrent evaluation of composite endpoints across multiple chronic conditions (e.g., cardiovascular, renal, and cognitive) utilizing time-to-first-event and total-event analyses.