

THE ALLIANCE FOR
LONGEVITY INITIATIVES

The Multi-Disease Therapeutic Designation

A Coordination Pathway for Multi-Disease Drug Development

For inclusion in the PDUFA VIII Reauthorization

Executive Summary

This whitepaper proposes the Multi-Disease Therapeutic Designation (MDTD), a targeted regulatory framework for therapies intended to produce clinically meaningful benefit across two or more serious diseases. Existing expedited programs, including Breakthrough Therapy, Regenerative Medicine Advanced Therapy (RMAT), and Accelerated Approval remain organized principally around individual indications. MDTD would provide a coordinated pathway for a separate multi-disease development program, whether pursued through an integrated master protocol, parallel disease-specific studies, or sequential indication development, further advancing FDA's broader clinical trial modernization agenda.

MDTD would be eligible to sponsors after their program has advanced beyond an attractive multi-disease hypothesis, but early enough for enhanced FDA coordination to improve development materially. Eligibility would require (1) preliminary human evidence of efficacy or clinically meaningful benefit in a lead serious chronic disease; (2) a credible, candidate-specific biological and translational basis for expecting benefit in at least one additional serious chronic disease; and (3) an investigational new drug application (IND) in effect for its clinical development program in that additional disease. Safety, pharmacokinetics, or target engagement alone would not suffice, and the sponsor would not need to demonstrate substantial improvement over available therapy, as required for Breakthrough Therapy designation, or efficacy in the second disease before designation.

MDTD provides the structured pathway that operationalizes master protocols, facilitates early cross-center scientific engagement, and establishes dedicated expedited tracks for complex, multi-indication programs. It would create no new approval standard, require no new FDA office, and would establish a disciplined, accountable stage of regulatory engagement for therapies that have generated meaningful human evidence and demonstrated both a credible cross-disease rationale and a tangible commitment to additional clinical development, making the PDUFA VIII reauthorization an appropriate vehicle for this procedural reform.

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 developing therapeutic that act on shared upstream disease drivers to navigate disconnected review teams and redundant regulatory hurdles.

Commercial Precedent: SGLT2 Inhibitors and GLP-1 Receptor Agonists

We see both the promise of multi-disease therapeutics and the cost of regulatory friction most clearly in the clinical evolution of SGLT2 inhibitors and GLP-1 receptor agonists. Although early clinical data demonstrated that these therapies modulate systemic metabolic and vascular pathways relevant across multiple organ systems, sponsors had to expand labels largely one indication at a time, moving sequentially from type 2 diabetes to cardiovascular outcomes, chronic kidney disease, obesity, and metabolic liver disease (MASH) across separate review divisions. While stepwise label expansion remains a proven route, the lack of a formal cross-divisional designation delays coordinated planning, forces sponsors to manage fragmented division-level interactions, and slows the translation of validated multi-system benefits into parallel pivotal programs.

Structural Bottlenecks in Bespoke Multi-Disease Negotiations

Conversely, efforts to evaluate broad, multi-system risk reduction in a single bespoke study—such as the proposed Targeting Aging with Metformin (TAME) trial highlight the operational friction of negotiating novel composite endpoints across multiple divisions without a standardized statutory home. Absent a predictable cross-divisional mechanism, sponsors face an untenable binary choice: either absorb the prohibitive cost and timeline of negotiating a bespoke multi-organ trial from scratch, or accept years of sequential, siloed development. MDTD resolves this impasse by establishing a formal, predictable pathway that supports coordinated parallel or sequential single-indication programs alongside integrated designs where appropriate.

Institutional Precedent for Regulatory Adaptability

Importantly, the FDA has already demonstrated its institutional capacity to adapt review frameworks for upstream chronic disease biology. Within the FDA's Center for Veterinary Medicine (CVM), for example, the agency's determination that Loyal's canine longevity candidate met the "Reasonable Expectation of Effectiveness" standard under expanded conditional approval showed that regulators can rigorously evaluate mechanistic and translational evidence targeting age-related physiological decline. While human drug approval under CDER and CBER rightly requires human clinical efficacy and distinct statutory standards, the CVM precedent underscores a critical principle for policymakers: regulatory pathways can evolve to match modern translational biology without compromising scientific rigor. MDTD brings that same regulatory adaptability into the human drug framework through a disciplined, human-evidence-anchored designation.

Explicit Agency Recognition in FDA's FY27 Regulatory Science Priorities

Even more directly, the FDA itself has formally recognized the need to modernize regulatory science around shared chronic disease and aging biology. In its Fiscal Year 2027 Broad Agency Announcement for the Advanced Research and Development of Regulatory Science (*FDABAA-27-00123*), the FDA established **"Aging and Longevity" (Research Area 10)** as a dedicated priority area for human drugs—explicitly soliciting tools to evaluate "multimorbidity prevention frameworks," "intrinsic capacity," and biomarkers reflecting a "general aging factor which may account for shared biological pathways driving morbidity and functional decline." While the FDA is actively funding extramural research to build these scientific tools, the agency still lacks the formal statutory designation within Section 506 needed to coordinate cross-divisional review when sponsors bring these therapies into human clinical development. MDTD closes that gap between the FDA's forward-looking regulatory science agenda and its day-to-day review architecture.

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

To qualify for Multi-Disease Therapeutic Designation (MDTD), a sponsor must meet a robust, human-evidence-anchored standard: (1) preliminary clinical proof-of-concept evidence (such as Phase 1b or Phase 2a data, excluding safety, PK, or target engagement alone) in at least one serious chronic disease; (2) candidate-specific mechanistic and translational evidence, supported by nonclinical data, providing a credible bridge to at least one additional serious chronic disease in a distinct disease category; and (3) an effective (cleared) investigational new drug (IND) application for that second disease, establishing a clinical development commitment. Where formulations, routes, or doses differ between programs, sponsors must provide an adequate scientific bridge (CMC, nonclinical, or clinical exposure data). Designation applies strictly to preventative and disease-modifying risk-reduction claims, excluding the treatment of established, symptomatic multi-organ failure. Once designated, MDTD unlocks intensive cross-divisional coordination, shared safety and CMC cross-referencing, and rolling review.

2.1 Expedited INDs for Sequential and Parallel Indications

To foster clinical efficiency and reduce development redundancy, we propose that MDTD programs be prioritized for expedited IND across two operational tracks: (1) initial INDs utilizing an integrated Master Protocol to evaluate multiple chronic conditions simultaneously, and (2) subsequent INDs filed to initiate clinical development in sequential, secondary indications once initial proof-of-concept has been established. Whether a sponsor consolidates endpoints into a single integrated trial or launches coordinated parallel trials across distinct disease classes, advancing multi-disease risk-reduction programs requires navigating heightened cross-division complexity. Prioritizing both integrated Master Protocols and follow-on indication INDs by leveraging the drug's existing CMC, toxicology, and early clinical safety packages accelerates the launch of parallel pivotal trials and aligns directly with the agency's goal to modernize clinical development without duplicating foundational review work.

2.2 Integrating Emerging Measurement Framework

The pathway should accommodate emerging functional and multi-morbidity measures, including validated measures of intrinsic capacity, when supported for the proposed context of use. Such measures could complement disease-specific endpoints, but designation would not presume that any emerging measure is a validated surrogate endpoint.

2.3 Coordinated Parallel and Sequential Single-Indication Trial Architectures

MDTD would not require sponsors to run complex, multi-organ composite trials, and rather accelerate coordinated parallel or sequential single-indication trials—mirroring the proven clinical trajectory of GLP-1 receptor agonists and SGLT2 inhibitors. Following initial Phase 1b/2a proof-of-concept in the lead indication and clearance of a second IND, sponsors can execute separate, indication-specific pivotal trials in parallel or in rapid sequence. This architecture allows each trial to maintain its own disease-appropriate standard-of-care control arm, targeted patient population, and clean statistical powering without requiring multimorbid enrollment.

Across these coordinated programs, MDTD facilitates early cross-divisional alignment on FDA-aligned adaptive trial designs—including seamless Phase 2/3 transitions for sequential indications, interim sample-size re-estimation, and biomarker-guided enrichment alongside shared safety databases, harmonized translational biomarkers, and coordinated cross-divisional product labeling.

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 siloed regulatory architecture imposes a hidden "administrative tax" on multi-indication development, forcing sponsors to navigate disconnected review divisions and file duplicative foundational packages for each organ system. MDTD eliminates this redundancy across both development tracks—whether a sponsor elects a single integrated Master Protocol with a shared Statistical Analysis Plan (SAP) or conducts coordinated parallel single-indication trials. By establishing a single cross-divisional regulatory home, enabling cross-referencing of existing CMC and nonclinical safety data, and prioritizing Expedited INDs for sequential indications, MDTD allows sponsors to generate pivotal clinical data in parallel rather than

sequentially. This compresses overall trial cycle times, protects patent runway, and ensures venture and R&D capital is directed toward patient trials rather than duplicative regulatory overhead.

3.3 Global Competitiveness and U.S. Biopharma Leadership

Regulatory predictability is a primary determinant of where next-generation chronic disease therapeutics are financed, tested, and commercialized. As international competitors aggressively subsidize translational chronic disease and healthy-aging research infrastructure, outdated single-disease review silos risk pushing early-stage clinical trials and biotech capital offshore. MDTD is a budget-neutral, high-leverage policy reform, requiring no new federal grant appropriations that modernizes FDA review workflows and anchors the next generation of multi-indication therapeutic development in the United States.

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.

Similarly, the Regenerative Medicine Advanced Therapy designation was established by the 21st Century Cures Act of 2016 as a targeted procedural reform within Section 506. Congress recognized that emerging cell and gene therapies did not fit neatly into legacy review frameworks and created a tailored designation to unlock early, cross-disciplinary FDA engagement without altering the statutory standard for safety and effectiveness.

Together, Breakthrough Therapy and RMAT provide the exact statutory blueprint for MDTD: Congress identified a structural gap in the existing review architecture and enacted a budget-neutral designation within Section 506 to bridge it. MDTD represents the logical next iteration of that precedent—modernizing cross-divisional coordination for therapeutics capable of preventing or modifying multiple serious chronic diseases.

5. Conclusion

Chronic diseases represent a dominant clinical and fiscal challenge forthe American healthcare system. Biomedical research increasingly identifies e shared biological mechanisms across these conditions, regulatory development remains organized primarily by individual indication

MDTD is a targeted, procedural response . It would create no new FDA office, authorize no product, and lower no safety or efficacy standard. It would establish a disciplined point of enhanced engagement for programs that have generated preliminary human efficacy in one serious chronic disease, developed a credible candidate-specific bridge to another, and placed a second clinical development program under an IND in effect.

The designation would support integrated multimorbidity trials where appropriate and coordinated sequential or parallel indication development where that model is more practical. In either case, a cross-divisional FDA team could address common scientific, CMC, nonclinical, clinical, and statistical issues while preserving the evidentiary requirements and benefit-risk determination applicable to each indication.

The Alliance for Longevity Initiatives respectfully urges the House Energy and Commerce Committee, the Senate Committee on Health, Education, Labor, and Pensions, 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.

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

(k) MULTI-DISEASE THERAPEUTIC DESIGNATION.—

(1) IN GENERAL.— At the request of the sponsor of a drug, the Secretary shall designate the drug as a multi-disease therapeutic if—

(A) PRELIMINARY HUMAN EFFICACY IN AN ANCHOR DISEASE.— The drug is supported by preliminary clinical evidence of therapeutic efficacy (such as Phase 1b or Phase 2a clinical data) in at least one serious chronic disease or condition, provided that safety, pharmacokinetic, or target-engagement data alone shall not be sufficient to satisfy this subparagraph;

(B) CANDIDATE-SPECIFIC BIOLOGICAL BRIDGE.— Candidate-specific mechanistic and translational evidence, supported as appropriate by nonclinical data, provides a credible scientific basis for expecting clinically meaningful benefit in at least one additional serious chronic disease or condition;

(C) ACTIVE SECOND CLINICAL DEVELOPMENT PROGRAM.— An investigational new drug application under section 505(i) or section 351(a)(3) of the Public Health Service Act is in effect for the investigation of the drug in such additional serious chronic disease or condition; and

(D) PRODUCT AND EXPOSURE CONTINUITY.— Where the drug investigated under subparagraph (C) differs in formulation, route of administration, dosing regimen, or systemic exposure from the drug evaluated under subparagraph (A), the sponsor provides an adequate scientific bridge (including applicable chemistry, manufacturing, and controls, nonclinical, or clinical bridging data) linking the two programs.

(2) REQUEST FOR DESIGNATION.— A sponsor may request designation under paragraph (1) concurrently with, or at any time after, the effective date of the investigational new drug application described in paragraph (1)(C).

(3) ACTIONS.— If the Secretary finds that the drug meets the criteria under paragraph (1), the Secretary shall designate the drug as a multi-disease therapeutic and shall take appropriate actions to expedite the development and review of applications for approval of such drug across relevant review divisions, including—

(A) assigning a cross-disciplinary project lead and convening a cross-divisional review team across applicable therapeutic divisions to coordinate End-of-Phase-2, Phase 3 design, and pre-NDA or pre-BLA interactions;

(B) providing timely advice and interactive communication to ensure efficient clinical development across initial and sequential indications, including cross-referencing of shared chemistry, manufacturing, and controls (CMC) and nonclinical safety data;

(C) expediting the review and clearance of subsequent investigational new drug applications (or protocol amendments) for additional serious chronic diseases or conditions, including by—

(i) prioritizing pre-IND consultations across relevant review divisions; and

(ii) permitting full cross-referencing of existing chemistry, manufacturing, and controls (CMC), nonclinical toxicology, and clinical safety data to eliminate duplicative review;

(D) facilitating flexible and pre-specified adaptive trial designs, including seamless Phase 2/3 transitions and coordinated parallel or sequential single-indication clinical trials; and

(E) involving senior managers and experienced review staff in collaborative, cross-disciplinary review and permitting rolling review of marketing applications.

(4) RULES OF CONSTRUCTION.— Nothing in this subsection shall be construed to—

(A) require a sponsor to demonstrate substantial improvement over available therapy in order to receive designation under paragraph (1);

(B) require a sponsor to conduct a single multi-morbidity clinical trial or enroll patients with concurrent multi-morbidity; or

(C) permit designation based solely on multiple favorable biomarker changes within a single disease or condition.

(5) DEFINITION AND SCOPE OF SERIOUS CHRONIC DISEASES.—

(A) IN GENERAL.— In this subsection, the term "serious chronic disease or condition" includes cardiovascular disease, type 2 diabetes, obesity and metabolic dysfunction, metabolic dysfunction-associated steatohepatitis (MASH), chronic kidney disease, Alzheimer's disease and related dementias, idiopathic pulmonary fibrosis, osteoarthritis, sarcopenia, and age-related macular degeneration, as further specified in guidance.

(B) INDEPENDENT CLINICAL INDICATIONS.— Distinct chronic diseases or conditions within the cardiometabolic, renal, or hepatic spectrum (such as type 2 diabetes, chronic kidney disease, and MASH) shall qualify as separate serious chronic diseases or conditions under paragraph (1), provided that each targeted indication represents a bona fide, independently meaningful clinical disease state rather than secondary biomarker improvements within a single condition.

(6) GUIDANCE.— Not later than 18 months after the date of enactment of this subsection, the Secretary shall issue draft guidance specifying—

(A) standards for preliminary clinical efficacy, candidate-specific translational bridging, and formulation/exposure continuity under paragraph (1); and

(B) procedures for cross-divisional review coordination, expedited review of subsequent investigational new drug applications, adaptive and parallel trial architectures, and evaluation of standardized functional endpoints (such as validated Intrinsic Capacity scores).