THE ALLIANCE FOR
LONGEVITY INITIATIVES

The Multi-Disease Prevention Designation

A Coordination Pathway for Integrated Prevention Trials in Age-Related Chronic Disease

For inclusion in the PDUFA VIII Reauthorization

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Executive Summary

This whitepaper proposes the Multi-Disease Prevention Designation (MDPD), a new regulatory framework designed to modernize how the FDA evaluates therapies that target the shared biological drivers of chronic disease. While the FDA's existing expedited pathway such as Breakthrough Therapy Designation and Accelerated Approval have transformed drug development, they remain rooted in a "one drug, one disease" model. This legacy architecture is optimized for reactive disease management: treating patients only after they cross a clinical threshold. MDPD provides a regulatory home for integrated prevention trials—studies designed not merely to manage existing symptoms, but to demonstrate that a single intervention can prevent the onset or progression of multiple age-related conditions simultaneously. This designation serves as a critical administrative vehicle for advancing the FDA's strategic initiatives for clinical trial modernization. It provides the structured pathway necessary to implement Master Protocols, foster early scientific engagement, and prioritize expedited IND tracks for complex, multi-indication development programs. To ensure focus and regulatory rigor, MDPD is a narrow, mechanism-based framework. It does not create a generalized "healthspan" or "aging" indication. Instead, it is strictly for programs that prospectively specify and power disease-specific or composite outcomes across a finite, serious list of chronic conditions, with labeling anchored in those validated clinical endpoints. The upcoming PDUFA VIII reauthorization is the natural legislative vehicle for this strategic alignment of FDA oversight with the convergent biology of modern medicine.

1. The Regulatory Mismatch

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 of aging share a common set of mechanistic drivers — the so-called hallmarks of aging: 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 — geroprotective compounds — 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 Aging with Metformin (TAME) trial as the first multi-disease prevention trial designed around shared aging 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 aging offers a unique window for "upstream" interception. MDPD identifies the regulatory infrastructure needed to capitalize on this window, shifting the focus from late-stage disease management to early-stage prevention.

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 prevention of age-related 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 prevention 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 lifespan-extension drug. If a regulatory pathway for multi-disease prevention is already operational for veterinary medicine, the institutional mechanism to regulate this class of science

is inherently feasible for human use. MDPD 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 MDPD, a sponsor must prospectively specify a development program where the primary objective is the prevention of incident disease events or the reduction of risk across two or more conditions from a defined, statutory list of serious age-related chronic diseases (e.g., composite incidence of MACE plus renal events). This designation is restricted to risk-reduction and prevention claims; it does not apply to the treatment of established, symptomatic multi-organ failure. This proposal positions the Multi-Disease Prevention Designation (MDPD) not as an isolated regulatory add-on, but as a critical infrastructure component for the FDA's ongoing clinical trial modernization efforts. MDPD serves as the administrative mechanism to execute three key objectives for regulatory efficiency: The MDPD 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 Geroscience-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 geroscience be formally designated as the primary network of QRIs for the MDPD 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. MDPD provides the regulatory infrastructure to operationalize this for geroscience. An MDPD program is defined by its use of a single, integrated "Master Protocol" that tracks multiple age-related 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 Longevity Modalities

To foster clinical efficiency and reduce development redundancy, we propose that MDPD 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 prevention 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 MDPD 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. MDPD provides the regulatory "landing zone" for these innovations. By allowing sponsors to utilize ARPA-H-validated IC scores as prospective surrogate endpoints within an MDPD Master Protocol, the FDA can replace traditional, decades-long outcomes trials with more efficient, functional measures of healthspan. Aligning the MDPD 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 longevity ecosystem.

2.5 Integrated Prevention Trial Design

An MDPD-eligible program typically employs a 5–7 year seamless, multistage, randomized trial in older 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 MDPD 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, preventive health. 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. MDPD provides the regulatory foundation for therapies that prevent the onset of multiple conditions, shifting the system from reactive management to cost-avoiding prevention.

3.2 Administrative and Trial Efficiency

The current regulatory architecture imposes a hidden "administrative tax" on multi-indication development. MDPD 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 geroprotective drug development is anchored. Other nations are aggressively investing in aging-focused research infrastructure. MDPD 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 Prevention 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 MDPD: Congress identified a gap in the existing architecture and added a targeted provision. The MDPD provision is the next iteration of that pattern for therapies targeting shared biology across multiple serious age-related chronic diseases.

4.2 PDUFA VIII Is the Right Vehicle, But Not The Only One

The PDUFA VIII reauthorization covers FDA fiscal years 2028 through 2032. FDA-industry technical negotiations concluded on May 15, 2026; the agreed package is moving toward congressional transmittal by the January 2027 statutory deadline, and reauthorization must be enacted by September 30, 2027 to avoid a funding lapse. The bill that ultimately carries the reauthorization will, on historical pattern, also carry substantive policy provisions added by the committees of jurisdiction — House Energy and Commerce and Senate HELP — beyond the FDA-industry technical agreement itself.

The MDPD provision fits that category cleanly. It is a procedural reform within FDA's existing authority and budget, structured as a separate expedited designation. It requires no new appropriation. It sits within the committees' jurisdiction. It has visible bipartisan support through the bipartisan Congressional Longevity Science Caucus. The legislative window for committee work runs from late 2026 through mid-2027. Now is the time to assemble bill text, build endorsement coalitions, and engage the relevant subcommittee staff.

While PDUFA VIII represents the most durable legislative vehicle for enacting MDPD, it is not the exclusive pathway. Many of the coordination efficiencies sought by this proposal such as the creation of cross-center review teams or the adoption of integrated protocol standards could be achieved through internal FDA administrative action, guidance documents, or a targeted Executive Order. An administrative approach offers the advantage of speed, but the legislative route remains the optimal vehicle for achieving a permanent, statutory foundation for the MDPD framework, ensuring these modernization efforts are insulated from shifts in administrative policy.

5. Addressing Objections

- **"This lowers the FDA's standard for approval."** The provision creates a coordination mechanism for development—not a lowering of the safety or efficacy bar. Sponsors must still demonstrate substantial evidence of effectiveness and safety for each indication.
- **"FDA lacks the workload capacity."** MDPD is workload-neutral. By standardizing multi-disease prevention programs through a single, integrated protocol, the agency avoids the redundant, ad-hoc negotiations currently required for separate indication expansions.
- **"Aging biomarkers are not mature enough."** It directs the agency to leverage existing pathways—such as the FDA's formal Biomarker Qualification Program (BQP)—including those currently being refined with ARPA-H—and ensures that all measures strictly adhere to the rigorous standards defined in the FDA-NIH BEST (Biomarkers, EndpointS, and other Tools) Resource.

- **“This will produce scope creep.”** The qualifying criteria are strict: the therapy must target shared biological drivers as the primary mechanism for preventing multiple conditions simultaneously. FDA retains full discretion to deny designation requests that do not meet these stringent mechanistic requirements.

6. Conclusion

The chronic diseases of aging 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 Prevention Designation (MDPD) 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 prevent the 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.

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 Prevention Designation in the PDUFA VIII reauthorization package.