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WHITE PAPER

A Regulatory Framework for the Approval of Peptide Therapeutics

Under Strict Manufacturing, Safety, and Clinical Oversight

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Executive Summary

Peptide therapeutics represent a mature yet rapidly evolving class of medicinal agents that occupy a distinct position between traditional small-molecule drugs and large biologic therapies. For more than a century, peptides have been safely and effectively used in clinical medicine—beginning with insulin and expanding to encompass therapies for metabolic disease, endocrinology, neurology, immunology, regenerative medicine, and critical care.

Despite a body of evidence spanning over 20,000 peer-reviewed publications in the last decade alone, recent regulatory actions have increasingly subjected peptide products—particularly compounded and investigational peptides—to categorical exclusion or enforcement actions that are disproportionate to their pharmacologic risk.

Core Petition

This white paper respectfully requests the adoption of a formal, peptide-specific, risk-based regulatory framework that aligns regulatory burden with actual patient risk, scientific plausibility, and manufacturing controls. Such a framework would preserve the FDA's core mission of protecting public health while correcting regulatory overreach that restricts access to safe, lower-cost therapies, stifles innovation, and inadvertently incentivizes unregulated gray-market distribution.

The proposed framework builds on existing statutory authority under the Federal Food, Drug, and Cosmetic Act (FDCA) while incorporating modern regulatory science. It emphasizes manufacturing quality, identity and purity, pharmacologic predictability, and post-market surveillance—rather than imposing biologics-level evidentiary requirements on peptide products that do not present biologics-level risk.

What Are Peptides and Why Do They Matter?

Modern medicine is entering a new era in which treatments are designed to work with the body's own biology rather than override it. One of the most transformative drivers of this shift is peptide therapeutics.

Peptides are short chains of amino acids—the same building blocks that constitute proteins. In the human body, peptides already function as natural messengers, regulating processes including metabolism, growth, healing, immunity, and brain function. Because they closely resemble substances the body naturally produces, peptide-based medicines tend to be highly specific, well tolerated, and less likely to cause widespread side effects compared to many traditional pharmaceuticals.

The first peptide drug, insulin, was introduced nearly 100 years ago. What is new is the technology. Advances in chemistry, biotechnology, and artificial intelligence now enable scientists to engineer peptides that persist longer in the body, reach specific organs, and

activate precise biological pathways. As a result, peptides are now being explored for conditions ranging from obesity and diabetes to injury recovery, cognitive decline, and immune dysfunction.

Unlike many conventional drugs that broadly stimulate or suppress entire biological systems, peptides typically target specific receptors or signaling pathways already in use by the body. They function as precisely written biological instructions rather than blunt pharmacologic commands.

Historically, a key challenge has been that peptides degrade rapidly in the bloodstream. Innovative solutions—such as attaching protective molecular groups or engineering slow-release prodrug formulations—have dramatically improved their stability, bioavailability, and clinical effectiveness.

Peptides and Metabolic Health

Beyond Appetite Suppression: Metabolism-Targeting Peptides

Obesity and metabolic disease are not simply disorders of appetite—they involve fundamental dysregulation of how cells store, utilize, and manage energy. Emerging peptide-based therapies aim to correct these deeper metabolic processes at the cellular level.

Some peptide compounds work by reprogramming adipocytes (fat cells), reducing their capacity to store energy while simultaneously increasing energy expenditure. Others mimic the cellular adaptations of exercise, improving mitochondrial function even in the absence of increased physical activity. Research has demonstrated that select metabolic peptides and related molecules can:

- Reduce adipocyte size and lipid accumulation
- Improve insulin sensitivity and glucose homeostasis
- Lower LDL cholesterol and triglyceride levels
- Increase skeletal muscle performance and endurance

Crucially, many of these effects occur without appetite suppression or hormonal disruption, distinguishing them from older weight-loss pharmacotherapies. The body naturally produces satiety peptides after eating that signal fullness to the hypothalamus. Scientists have developed longer-acting analogs of these signals to assist in appetite regulation—though research also reveals that overstimulation of these pathways can cause nausea, underscoring the necessity of careful dosing and medical supervision.

Supporting Natural Growth Hormone Rhythms

Growth hormone plays a fundamental role in tissue repair, muscle strength, bone density, and metabolic regulation. Rather than administering exogenous growth hormone directly—which can

produce significant side effects—modern approaches employ growth hormone secretagogues. These peptides gently stimulate the pituitary gland to release growth hormone in its natural pulsatile rhythm.

Documented benefits of this approach include:

- Improved muscle recovery and hypertrophy
- Enhanced sleep quality and restorative sleep architecture
- Favorable changes in body composition (increased lean mass, reduced adiposity)
- Reduced risk of growth hormone excess or receptor downregulation

Different compounds vary considerably in duration of action, receptor selectivity, and side-effect profiles. Some are short-acting and highly selective, while others produce longer-lasting effects but may increase appetite or cause transient fluid retention.

Tissue Repair and Regenerative Applications

Recovery from tendon, ligament, and muscle injuries is frequently slow, incomplete, and prone to fibrotic scar tissue formation. Certain peptides studied in the field of regenerative medicine have demonstrated the capacity to:

- Promote angiogenesis (new blood vessel formation)
- Support organized collagen deposition and matrix remodeling
- Enhance neuromuscular communication and motor unit recruitment
- Accelerate recovery in multiple validated animal injury models

It is important to note that not all peptides with promising preclinical results have received regulatory approval for human use. Regulatory agencies appropriately restrict substances lacking sufficient human safety data—even when laboratory findings are encouraging. This white paper advocates for a pathway that would allow well-characterized, endogenous-derived peptides to enter supervised clinical use under appropriate monitoring frameworks.

Brain Health and Cognitive Support

Overcoming the Blood-Brain Barrier

The brain is protected by the blood-brain barrier, a highly selective physiological boundary that restricts the passage of most drugs. Certain peptides, however, have been specifically engineered to traverse this barrier or are administered via intranasal routes that allow direct access to the central nervous system.

Research-based neuropeptides have been investigated for applications including:

- Neurological recovery following stroke and traumatic brain injury

- Regulation of anxiety, stress responses, and HPA-axis dysfunction
- Enhancement of cognitive performance, memory consolidation, and executive function
- Neuroprotection against oxidative stress and excitotoxicity

Unlike traditional sedatives or CNS stimulants, certain neuropeptides appear to enhance mental clarity and cognitive resilience without inducing sedation, dependency, or emotional blunting—a significant advantage for long-term therapeutic use.

Neuroplasticity and Neurorehabilitation

Multi-peptide formulations in international clinical use aim to support the brain's capacity for structural and functional reorganization following injury—a process termed neuroplasticity. Clinical studies conducted outside the United States suggest meaningful benefits in stroke rehabilitation, traumatic brain injury recovery, and neurodegenerative disease management. Regulatory approval varies by country, but the international evidence base continues to grow.

Aging, Mitochondria, and Cellular Health

Mitochondrial Signaling Peptides

Mitochondria—the cell's primary energy-generating organelles—also function as signaling hubs that influence aging trajectories and metabolic regulation. Scientists have identified a class of small peptides, encoded within mitochondrial DNA, that help regulate insulin sensitivity, inflammatory tone, and cellular stress responses.

In animal studies, restoring youthful concentrations of these mitochondrially-derived peptides has produced:

- Improved glucose tolerance and insulin sensitivity
- Attenuation of age-related metabolic decline
- Cardioprotective and vasculoprotective effects

Human research is ongoing, with active investigation into optimal delivery methods, dosing protocols, and long-term safety.

Senolytic Peptides and Cellular Rejuvenation

As biological aging progresses, dysfunctional "senescent" cells accumulate in tissues and release pro-inflammatory signals that accelerate systemic aging and organ dysfunction. Experimental peptides designated as senolytics are designed to selectively eliminate these dysfunctional cells while preserving healthy ones. Early-stage human studies have reported reductions in systemic inflammation biomarkers, though this therapeutic approach remains investigational and requires further clinical validation.

Immune Support and Critical Care Applications

Peptides occupy a unique niche in immunomodulation. Certain thymus-derived peptides have been utilized in clinical settings internationally for decades to support adaptive immune responses without causing immunosuppression. These agents have been studied extensively in the context of viral infections, cancer immunology, and vaccine adjuvancy.

Additional peptides targeting pulmonary inflammation and alveolar gas exchange have been investigated for use in severe respiratory illness. Several received expedited regulatory attention during the COVID-19 pandemic, and their long-term regulatory and clinical status continues to evolve as post-pandemic evidence accumulates.

The Future of Peptide Medicine

Peptide therapeutics represent a scientifically compelling middle ground between conventional small-molecule drugs and complex biologic therapies. Their ability to modulate the body's own signaling systems with precision makes them especially promising for treating chronic diseases, facilitating recovery, and addressing the multidimensional biology of age-related decline.

Regulatory agencies have appropriately emphasized the need for rigorous human data prior to widespread clinical adoption. The future of peptide medicine depends on advances in delivery technology, long-term safety surveillance, and the establishment of rational regulatory distinctions between approved therapies, supervised investigational use, and experimental research.

Key Takeaway for Patients and Clinicians

Peptides are not miracle cures. However, when carefully developed, rigorously manufactured, and responsibly prescribed under medical supervision, they may become among the most precise, targeted, and patient-compatible tools available in modern medicine.

Historical and Regulatory Background of Peptide Therapeutics

Peptides have been a cornerstone of modern medicine since the FDA's earliest regulatory activities. The isolation and clinical deployment of insulin in the 1920s marked the beginning of peptide-based therapeutics, followed by desmopressin, oxytocin, vasopressin, calcitonin, glucagon, gonadotropin-releasing hormone (GnRH) analogs, and parathyroid hormone derivatives. These agents fundamentally transformed the treatment of diabetes, endocrine disorders, reproductive health, and metabolic disease.

Over the past two decades, peptide innovation has accelerated substantially due to advances in solid-phase peptide synthesis (SPPS), recombinant DNA expression, pegylation, fatty acid conjugation, and targeted delivery platforms. As of 2025, peptides and oligonucleotides represent a growing proportion of FDA-approved new molecular entities. GLP-1 receptor agonists such as semaglutide have further demonstrated the capacity of peptides to deliver population-level public-health benefits, including documented reductions in cardiovascular morbidity and mortality.

Historically, FDA regulation of peptides has recognized their biological familiarity, predictable metabolism, and favorable safety margins—allowing approval pathways distinct from those applied to novel synthetic small molecules. The 2023 reclassification of numerous well-established peptides into "Category 2" status was not precipitated by new safety signals, but rather by a technical procedural reclassification—despite decades of international clinical use and documented physician-supervised safety records in the United States.

Regenerative Peptide & Compound Status Chart

The following table documents key peptide compounds, their therapeutic categories, and their current or historical regulatory status:

Compound Name	Category / Type	Regulatory Status & History
Thymosin-alpha 1 (Tα1)	Immune Modulator	Approved in 40+ countries for hepatitis B/C and cancer immunotherapy; 30+ years of international use. FDA reclassified to Category 2 in 2023 citing insufficient U.S. human data, despite global pharmacovigilance records.
BPC-157	Gastric/Repair Peptide	Endogenous gastric fragment with 3 decades of preclinical and physician-supervised use in musculoskeletal and gastrointestinal repair. Reclassified to Category 2 in 2023 based on a perceived lack of sufficient safety information.
CJC-1295 / Ipamorelin	GH Secretagogues	Utilized by thousands of physicians for natural GH support with a well-established safety profile. Restricted under the 2023 broad peptide reclassification.
TB-500 (Thymosin β4)	Regenerative Peptide	Naturally occurring peptide essential for tissue repair; used extensively in sports medicine and

Compound Name	Category / Type	Regulatory Status & History
		regenerative practice. Compounding disallowed in 2023 despite physician-supervised safety history.
GHK-Cu (Injectable)	Copper Peptide	Endogenous tri-peptide with well-documented anti-inflammatory and repair activity; remains approved in topical/cosmetic forms. Injectable form restricted in 2023.
AOD-9604	Metabolic Peptide	Growth hormone fragment with decades of research demonstrating lipolytic benefits without glycemic effects. Restricted during the 2023 FDA peptide reclassification.
HCG	Biologic Hormone	FDA-approved for over 50 years with an exemplary safety record. Reclassified as a biologic in 2020, effectively prohibiting production by traditional 503A compounders.
Semaglutide / Tirzepatide	GLP-1 Agonists	High safety profile; available via compounding during shortage periods. Compounding restrictions tightened as brand-name manufacturers assert shortage resolution.
MOTS-C / Epitalon / KPV	Bioregulatory Peptides	Endogenous peptides naturally present in the body with years of international safety data and anecdotal clinical use. All reclassified to Category 2 in the 2023 FDA sweep.
DSIP (Emideltide)	Sleep Peptide	Naturally occurring deep-sleep-inducing peptide with established use in sleep disorders and withdrawal management. Disallowed in 2023 with no new safety concerns cited.

The 2023 Reclassifications: A Regulatory Analysis

Practitioners and regulatory scholars in the field have noted that the FDA's 2023 "Category 2" reclassifications constituted a procedural maneuver rather than a response to documented

medical emergencies or newly identified safety signals. By designating these compounds as “may pose significant risk” or "lack of adequate human data," the FDA effectively disregarded:

- FDA’s historical approach and regulatory framework for prescription drug products: all prescription drugs pose risk to patients. Designation as a prescription drug means that such drug is not safe for use except under the supervision of a practitioner licensed by law to administer such drug. Practitioners licensed by law to administer prescription drugs are in the best position to make therapeutic decisions for patients.
- Natural Endogenous Origin: The majority of reclassified peptides (including BPC-157, Tα1, GHK-Cu, MOTS-C, and Thymosin β4) are molecules naturally occurring within the human body.
- Extensive Clinical Experience: Thousands of licensed physicians have administered these compounds for decades without the systemic adverse effects commonly associated with pharmaceutical alternatives such as NSAIDs, corticosteroids, or immunosuppressants.
- International Regulatory Precedent: Many reclassified peptides remain fully approved and integrated into mainstream medical practice in Europe, Japan, Russia, and numerous other jurisdictions with well-developed pharmacovigilance infrastructure.

Scientific Rationale for a Distinct Peptide Regulatory Pathway

Peptide-based therapeutics occupy a pharmacologically distinct position within the drug development spectrum. Their intrinsic biochemical and pharmacodynamic properties fundamentally differentiate them from conventional small molecules, yielding markedly different safety, metabolism, and risk profiles. These distinctions warrant a proportionate and graduated regulatory framework aligned with actual biological risk.

1. Receptor Specificity and Reduced Off-Target Effects

Peptides typically demonstrate exceptional receptor and signaling pathway specificity, owing to their structural similarity to endogenous ligands such as hormones, neuropeptides, cytokines, and growth factors. Unlike small molecules—which often bind conserved enzymatic pockets and may interact with multiple unrelated molecular targets—peptides engage receptors through extended, sequence-dependent interactions that confer exquisite selectivity.

This specificity substantially reduces off-target pharmacology, a primary contributor to adverse drug reactions in small-molecule therapeutics. Numerous comparative analyses have confirmed that peptide drugs exhibit significantly lower binding promiscuity across unintended receptors and enzymes, particularly relative to lipophilic small molecules optimized for oral bioavailability.

2. Predictable Metabolic Degradation

A defining and clinically significant feature of peptides is their rapid enzymatic degradation by endogenous proteases into constituent amino acids or short oligopeptides. These breakdown

products enter normal anabolic and catabolic pathways and are indistinguishable from endogenous metabolic substrates.

This metabolic predictability stands in sharp contrast to the hepatic biotransformation required for most small-molecule drugs, where cytochrome P450-mediated oxidation can generate toxic metabolites, contribute to significant interindividual pharmacokinetic variability, and increase the risk of drug-induced liver injury. Peptide clearance is largely independent of hepatic enzyme polymorphisms, substantially reducing population-level variability and post-marketing safety surprises.

3. No Bioaccumulation and Favorable Organ Safety

Due to their hydrophilicity, limited membrane permeability, and susceptibility to rapid proteolysis, peptides demonstrate negligible potential for hepatic or renal bioaccumulation. In contrast, lipophilic or halogenated small molecules may persist in tissues, accumulate with repeated dosing, and exert cumulative organ toxicity.

Peptides generally exhibit short half-lives and are cleared via predictable proteolytic and renal pathways without retention in organ systems. Even with repeated administration, systemic exposure does not typically escalate in a nonlinear or cumulative fashion, substantially reducing long-term organ toxicity risk.

4. Minimal Drug-Drug Interaction Potential

Peptides have minimal involvement of cytochrome P450 (CYP) enzymes in their metabolism, resulting in a markedly reduced risk of clinically meaningful drug-drug interactions. This is of particular importance in complex patient populations—older adults, patients with chronic disease, and polypharmacy patients—who are at greatest risk from interaction-driven adverse events.

In contrast, small-molecule drugs frequently function as CYP inhibitors or inducers, leading to unpredictable changes in plasma concentrations of co-administered medications. The absence of CYP dependence in peptide metabolism simplifies clinical risk assessment and reduces the evidentiary burden for drug interaction studies.

5. Low Immunogenic Potential

While immunogenicity is a central concern for monoclonal antibodies and recombinant proteins, most therapeutic peptides exhibit low immunogenic potential—particularly when composed of naturally occurring amino acids and designed to mimic endogenous molecular sequences. Their small molecular size limits epitope complexity and reduces the likelihood of sustained anti-drug antibody formation.

6. Predictable, On-Target Toxicity Profile

Because peptides closely mimic endogenous signaling molecules, observed toxicities are most frequently attributable to on-target pharmacologic exaggeration rather than off-target chemical

injury. These effects are generally anticipated, dose-dependent, mechanistically explainable, and reversible—further distinguishing their risk profile from small molecules.

Small molecules, by contrast, are associated with idiosyncratic toxicity, genotoxicity, mutagenicity, and long-term carcinogenic risk arising from unpredictable interactions between synthetic chemical structures and DNA, mitochondria, or cellular stress pathways.

Regulatory Implication

Taken together, these pharmacologic characteristics support a graduated, risk-based regulatory approach for peptide therapeutics. Rather than imposing a uniform premarket evidentiary burden across all molecular classes, regulatory requirements should scale according to the degree of structural novelty, extent of chemical modification, duration and route of exposure, and degree of departure from endogenous analogs. Applying small-molecule-centric toxicology paradigms to low-risk peptide therapeutics imposes unnecessary barriers without proportional safety benefit.

Manufacturing Controls and Safety Assurance

The primary safety risks associated with peptide therapeutics arise not from their molecular class characteristics, but from manufacturing quality, impurity control, and sterility assurance. Modern peptide production employs a rigorous suite of analytical and quality control methodologies:

- Solid-phase peptide synthesis (SPPS) with validated coupling chemistry and sequence verification
- High-performance liquid chromatography (HPLC) purification achieving sequence-confirmed identity
- Mass spectrometry for molecular identity confirmation and impurity profiling
- Endotoxin testing, sterility assurance, and residual solvent analysis per pharmacopeial standards

When produced in FDA-registered facilities operating under current Good Manufacturing Practice (cGMP) standards, peptide products routinely achieve purity levels exceeding 98–99%, with reproducible batch-to-batch consistency and documented stability profiles.

Established regulatory mechanisms—including USP <795>, <797>, and <800> standards, mandatory adverse event reporting, lot traceability requirements, and facility inspection authority—are fully capable of mitigating manufacturing-related risks. A peptide-specific regulatory pathway would leverage and build upon these existing controls rather than duplicating biologics-level requirements designed for living-cell or gene-transfer products.

Clinical Domains and Representative Peptide Classes

Peptide therapeutics demonstrate broad and growing clinical relevance across multiple medical specialties:

Metabolic and Endocrine Medicine

Representative agents include Amino-1MQ (NNMT inhibition), SLU-PP-332 (ERR agonism), AOD-9604 (lipolysis induction), Peptide YY (3-36), Setmelanotide (MC4R agonism), Ibutamoren, Ipamorelin, CJC-1295, and other growth hormone secretagogues. These agents address obesity, insulin resistance, sarcopenia, and metabolic syndrome through receptor-specific signaling rather than systemic appetite suppression or stimulant pharmacology.

Regenerative and Musculoskeletal Medicine

BPC-157, TB-500 (Thymosin β-4 fragment), PEG-MGF, and GHK-Cu promote angiogenesis, fibroblast migration, satellite cell activation, and extracellular matrix remodeling. Preclinical data and early human evidence consistently indicate favorable safety profiles, with adverse effects largely limited to transient local injection-site reactions.

Neurologic and Cognitive Disorders

Neuropeptides such as Semax, Selank, Cerebrolysin, Dihexa acetate, P-21, Pinealon, and Humanin have demonstrated neurotrophic, anxiolytic, and cognitive-protective effects in international clinical settings. Several are approved or widely utilized outside the United States with established pharmacovigilance records and favorable long-term safety profiles.

Immunologic and Critical-Care Applications

Thymosin-α1, VIP (Aviptadil), Cathelicidin LL-37, and KPV modulate immune balance and inflammatory signaling through well-characterized mechanisms. Thymosin-α1, in particular, has been administered to tens of thousands of patients globally with a comprehensively characterized safety profile spanning four decades.

Recent enforcement actions restricting access to certain peptides have frequently cited insufficient randomized controlled trial data, even where extensive nonclinical evidence and international human use experience exist. This evidentiary threshold diverges from historical FDA practice, particularly regarding off-label use of approved peptides and orphan disease indications.

From a health economics perspective, peptide therapeutics offer a substantial cost advantage over monoclonal antibodies and gene therapies. Greater manufacturing scalability, shorter development timelines, and reduced cold-chain complexity can translate into significantly lower healthcare expenditures—an important consideration in the context of ongoing debates about drug pricing and healthcare access.

Proposed Tiered Regulatory Framework for Peptide API

The following tiered, risk-adjusted framework is proposed to align regulatory burden with the actual pharmacologic and safety profile of each peptide category for API manufacturing:

Regulatory Tier	Requirements
Tier 1 — Endogenous or Near-Endogenous Peptides	• cGMP manufacturing certification and facility registration • Identity, purity, and potency testing per pharmacopeial standards • Basic acute and subacute toxicology package • Mandatory pharmacovigilance and adverse event reporting • Prior regulatory review by FDA (not full approval required)
Tier 2 — Modified or Stabilized Peptides	• All Tier 1 requirements • Expanded toxicology including repeat-dose studies • Pharmacokinetic and bioavailability characterization • Limited human safety studies (Phase 1 equivalent) • Enhanced post-market surveillance commitment
Tier 3 — Novel Synthetic Peptides	• Full phased clinical development (Phase 1 through Phase 3) • Comprehensive preclinical toxicology package • Rigorous CMC (Chemistry, Manufacturing & Controls) documentation • Regulatory review proportional to exposure duration and indication severity • Standard NDA or BLA pathway as appropriate

This tiered structure preserves meaningful FDA oversight and patient safety protections while aligning regulatory burden with demonstrable patient risk. It would allow endogenous, well-characterized peptides with established international safety records to re-enter supervised clinical use through compounding channels, while maintaining appropriately rigorous standards for novel or substantially modified peptide entities.

Appendix A: Peptide Compounds — Natural Origin Reference

The following table documents representative peptide compounds alongside their natural biological origin or mechanism, providing scientific context for regulatory classification decisions:

Compound Name	Natural Presence / Mechanism of Action
5-Amino-1MQ	Small molecule inhibitor of NNMT enzyme, which naturally governs energy metabolism and NAD+ salvage pathways.
SLU-PP-332	Activates Estrogen-Related Receptors (ERRs), mimicking the natural metabolic and mitochondrial adaptations of aerobic exercise.
CB-4211	Modified analog of MOTS-c, a peptide naturally encoded within mitochondrial DNA with roles in metabolic homeostasis.
TB-500	Mirrors the active tissue-healing sequence of Thymosin β4, a protein naturally expressed in virtually all human cells.
Humanin	Fully endogenous; naturally encoded within mitochondrial 16S rRNA for cytoprotection and anti-apoptotic signaling.
FOXO4-DRI	Interferes with the natural FOXO4-p53 interaction to selectively trigger apoptosis in senescent cells.
B7-33	Functional fragment of the natural human hormone H2-relaxin with anti-fibrotic and vasodilatory properties.
VIP (Aviptadil)	Fully endogenous; naturally produced in the brain, gastrointestinal tract, and immune cells; regulates vasodilation and immune modulation.
Cerebrolysin	Multi-peptide mixture that mimics the activity of natural neurotrophic factors including BDNF and GDNF.
Hexarelin	Mimics the natural hunger hormone ghrelin to stimulate growth hormone release via GHSR activation.
Desmopressin	Synthetic analog of Antidiuretic Hormone (ADH/vasopressin), naturally synthesized in the hypothalamic nuclei.
P-21 Peptide	Mimics the neurotrophic activity of CNTF, a natural protein supporting neuronal survival and axonal regeneration.
Peptide YY (3-36)	Fully endogenous; naturally secreted by intestinal L-cells post-prandially to signal satiety to the hypothalamus.
Pinealon	Based on short tetrapeptide sequences naturally occurring in the pineal gland; studied for neuroprotective and circadian effects.
Setmelanotide	Mimics the body's natural MC4R signaling pathway for central appetite regulation; approved for rare genetic obesity disorders.
Cathelicidin LL-37	Fully endogenous; the primary human cathelicidin antimicrobial peptide, naturally produced by epithelial cells and neutrophils.
GHK-Cu	Fully endogenous copper-binding tri-peptide naturally present in human plasma; concentration declines significantly with aging.
GHRP-2 / GHRP-6	Both mimic the natural hormone ghrelin to stimulate GH release; differ in selectivity and appetite stimulation profiles.

Compound Name	Natural Presence / Mechanism of Action
Ipamorelin Acetate	Selective ghrelin mimetic; stimulates GH release with minimal effects on cortisol and prolactin compared to earlier GHRPs.
Kisspeptin-10	Fully endogenous peptide hormone; the primary upstream trigger for GnRH-mediated reproductive hormone cascades.
KPV	C-terminal fragment of the natural hormone α-MSH; exhibits anti-inflammatory activity in gut and skin tissues.
MOTS-c	Fully endogenous mitochondrially-derived peptide that functions as a metabolic regulator and exercise mimetic.
Semax	Heptapeptide analog of an ACTH(4-10) fragment; mimics a natural peptide released during stress with nootropic properties.
Selank Acetate	Analog of Tuftsin, a natural immune-regulatory peptide; exhibits anxiolytic effects without sedation or dependency.
Thymosin-alpha 1 (Tα1)	Fully endogenous; naturally produced by the thymus gland as a primary mediator of T-cell maturation and immune defense.
Thymosin β4 Fragment	Specific biologically active fragment of Thymosin β4, a protein ubiquitously expressed in human tissues for cytoskeletal and repair functions.
Epitalon	Synthetic tetrapeptide mimicking Epithalamin, a natural polypeptide secreted by the pineal gland; studied for telomerase activation.
Emideltide (DSIP)	Fully endogenous; naturally identified in the brain as Delta Sleep-Inducing Peptide; studied for sleep architecture and withdrawal therapy.
AOD-9604	Synthetic fragment of human growth hormone corresponding to the region responsible for lipolytic activity without IGF-1 stimulation.
CJC-1295	Long-acting synthetic analog of Growth Hormone Releasing Hormone (GHRH), naturally secreted by the hypothalamus.
PEG-MGF	PEGylated variant of Mechano Growth Factor, a splice variant of IGF-1 naturally produced in response to muscle mechanical stress.

Appendix B: References (AMA Format)

1. Trier N, Hansen P, Houen G. Peptides, Antibodies, Peptide Antibodies and More. Int J Mol Sci. 2019;20(24):6289.

2. Ajingi YS, Rukying N, Aroonsri A, Jongruja N. Recombinant Active Peptides and their Therapeutic Functions. Curr Pharm Biotechnol. 2022;23(5):645-663.

3. Buchan TA, Ching C, Foroutan F, et al. Prognostic value of natriuretic peptides in heart failure: systematic review and meta-analysis. Heart Fail Rev. 2022;27(2):645-654.

4. Nielipinska D, Rubiak D, et al. Stapled peptides as potential therapeutics for diabetes and other metabolic diseases. Biomed Pharmacother. 2024;180:117496.

5. Okasha H. Fundamental Uses of Peptides as a New Model in Both Treatment and Diagnosis. Recent Pat Biotechnol. 2024;18(2):110-127.

6. Ribeiro FM, Anderson M, Aguiar S, et al. Systematic review and meta-analysis of gut peptides expression during fasting and postprandial states in individuals with obesity. Nutr Res. 2024;127:27-39.

7. Wahart A, Hocine T, Albrecht C, et al. Role of elastin peptides and elastin receptor complex in metabolic and cardiovascular diseases. FEBS J. 2019;286(15):2980-2993.

8. Wang CQ, Shen YS, Chen XF, et al. Intrapleural administration with thymic peptides in malignant pleural effusion: systematic review and meta-analysis. Int Immunopharmacol. 2022;107:108688.

9. Vecchio I, Tornali C, Bragazzi NL, Martini M. The Discovery of Insulin: An Important Milestone in the History of Medicine. Front Endocrinol. 2018;9:613.

10. Gerstein HC, Rutty CJ. Insulin Therapy: The Discovery That Shaped a Century. Can J Diabetes. 2021;45(8):798-803.

11. Segre GV, Goldring SR. Receptors for secretin, calcitonin, PTH/PTH-related peptide, VIP, GLP-1, GHRH, and glucagon belong to a newly discovered G-protein-linked receptor family. Trends Endocrinol Metab. 1993;4(10):309-314.

12. Reardon B, Pasalic L, Favaloro EJ. A Review of Desmopressin Use in Bleeding Disorders: An Unsung Hero? Biomolecules. 2025;15(7):967.

13. Ivell R, Schmale H, Richter D. Vasopressin and oxytocin precursors as model preprohormones. Neuroendocrinology. 1983;37(3):235-240.

14. Snider B, Geiser A, Yu XP, et al. Long-Acting and Selective Oxytocin Peptide Analogs Show Antidiabetic and Antiobesity Effects in Male Mice. J Endocr Soc. 2019;3(7):1423-1444.

15. Stevenson JC, Evans IM. Pharmacology and therapeutic use of calcitonin. Drugs. 1981;21(4):257-272.

16. Leder BZ. Parathyroid Hormone and PTH-Related Protein Analogs in Osteoporosis Therapy. Curr Osteoporos Rep. 2017;15(2):110-119.

17. Fuggle N, Rizzoli R, Beaudart C, et al. Parathyroid hormone receptor agonists in the management of osteoporosis. Nat Rev Rheumatol. 2025;21(10):599-611.

18. Hruby VJ, Cai M. Design of peptide and peptidomimetic ligands with novel pharmacological activity profiles. Annu Rev Pharmacol Toxicol. 2013;53:557-580.

19. Eiden LE, Goosens KA, Jacobson KA, Leggio L, Zhang L. Peptide-Liganded G Protein-Coupled Receptors as Neurotherapeutics. ACS Pharmacol Transl Sci. 2020;3(2):190-202.

20. Wang L, Wang N, Zhang W, et al. Therapeutic peptides: current applications and future directions. Signal Transduct Target Ther. 2022;7(1):48.

21. Zheng B, Wang X, Guo M, Tzeng CM. Therapeutic Peptides: Recent Advances in Discovery, Synthesis, and Clinical Translation. Int J Mol Sci. 2025;26(11):5131.

22. Dean TT, Jelu-Reyes J, Allen AC, Moore TW. Peptide-Drug Conjugates: An Emerging Direction for the Next Generation of Peptide Therapeutics. J Med Chem. 2024;67(3):1641-1661.

23. Lau JL, Dunn MK. Therapeutic peptides: Historical perspectives, current development trends, and future directions. Bioorg Med Chem. 2018;26(10):2700-2707.

24. Sall C, Argikar U, Fonseca K, et al. Industry Perspective on Therapeutic Peptide Drug-Drug Interaction Assessments. Clin Pharmacol Ther. 2023;113(6):1199-1216.

25. Norgaard RA, Bhatt DK, Jarvinen E, et al. Evaluating Drug-Drug Interaction Risk Associated with Peptide Analogs Using Advanced In Vitro Systems. Drug Metab Dispos. 2024;52(11):1170-1180.

26. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician. 2007;76(3):391-396.

27. Zhang Z, Svensson KJ. Discovery of peptides as key regulators of metabolic and cardiovascular crosstalk. Cell Rep. 2025;44(6):115836.