Reconsidering *the* FDA Restriction *of* Peptide Therapeutics

Scientific Evidence, Regulatory Context, and Policy Implications

Advocacy Brief for Policymakers and Healthcare Stakeholders

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Executive Summary

Peptide therapeutics represent one of the most rapidly expanding frontiers in contemporary biomedical science. As short chains of amino acids that function as signaling molecules within physiological systems, peptides often exhibit highly specific biological activity with favorable pharmacokinetic characteristics and comparatively low systemic toxicity when contrasted with many traditional small-molecule pharmaceuticals. These attributes have stimulated growing interest among clinicians and researchers in fields ranging from endocrinology and immunology to regenerative medicine and neurobiology, where peptide-based interventions may offer novel approaches to complex diseases.

In late 2023, the **U.S. Food and Drug Administration (FDA)** placed nineteen peptide substances into **Category 2** of the federal compounding list maintained under Section 503A of the Federal Food, Drug, and Cosmetic Act. Placement within Category 2 effectively prohibits licensed compounding pharmacies from preparing these substances for patient care because the agency determined that they may present significant safety risks. In support of this determination, the FDA cited concerns related to potential immunogenic responses associated with peptide administration, the possibility of impurities arising during peptide synthesis or degradation, and what the agency described as insufficient human safety data to justify routine compounding.

Despite these stated concerns, the scientific literature reveals a highly heterogeneous evidence base among the peptides affected by this regulatory action. Several of the compounds included in the restriction have documented human clinical exposure, peer-reviewed research, and ongoing investigative programs exploring therapeutic applications. Others remain earlier in the research continuum and may appropriately warrant additional study prior to broader clinical adoption. The aggregation of these diverse substances into a single regulatory category has therefore generated debate within the medical and scientific communities regarding whether the policy appropriately reflects the available evidence.

Critics of the decision argue that the FDA's action may have inadvertently grouped together peptides with dramatically different levels of clinical support, producing a regulatory outcome that restricts physician discretion and limits patient access to emerging therapeutic tools. At the same time, proponents of stricter oversight emphasize the importance of maintaining rigorous standards for pharmaceutical purity, safety, and manufacturing quality.

Recent public statements from **Robert F. Kennedy Jr.**, (JRE #2461) currently serving as Secretary of Health and Human Services, suggest that the peptide classifications may undergo review as part of broader discussions regarding regulatory transparency and innovation in biomedical therapeutics. Such a reassessment could provide an opportunity to evaluate each peptide according to its individual safety profile and clinical evidence, potentially allowing policymakers to better balance patient protection with the advancement of scientific and medical progress.

Regulatory Background

Drug Quality and Security Act

The modern regulatory framework governing pharmaceutical compounding in the United States originates from the Drug Quality and Security Act, enacted by Congress in response to the 2012 fungal meningitis outbreak linked to contaminated compounded medications. That public health crisis highlighted vulnerabilities in the oversight of compounding practices and prompted federal lawmakers to establish a

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more clearly defined regulatory structure designed to improve quality assurance, manufacturing accountability, and patient safety.

The legislation created two distinct categories of compounding facilities, each with its own regulatory responsibilities and scope of practice. These categories, commonly referred to as 503A compounding pharmacies and 503B outsourcing facilities, form the backbone of the United States compounding oversight system.

503A compounding pharmacies are traditional pharmacies that prepare medications in response to individual patient prescriptions issued by licensed healthcare providers. These facilities operate primarily under the authority of state boards of pharmacy and are expected to follow established compounding standards designed to ensure product identity, sterility, and purity. Their operations are limited to patient-specific prescriptions, and they are generally prohibited from manufacturing large batches of medications for broader distribution. Although 503A pharmacies must comply with established compounding standards, they are not required to operate under the full Current Good Manufacturing Practice (CGMP) regulations that govern large-scale pharmaceutical manufacturing.

In contrast, 503B outsourcing facilities were created to allow larger-scale compounding operations that could supply compounded medications directly to hospitals, surgical centers, and other healthcare institutions. These facilities are regulated at the federal level and must comply with CGMP manufacturing standards similar to those applied to pharmaceutical manufacturers. As part of these requirements, 503B facilities are subject to routine FDA inspections, must validate their manufacturing and stability processes, and must maintain rigorous control over the sourcing and testing of raw pharmaceutical ingredients used in their products.

The scientific and technical standards guiding the preparation of compounded medications are established by the United States Pharmacopeia, a nonprofit scientific organization that publishes internationally recognized quality standards for pharmaceutical substances. USP standards address critical aspects of pharmaceutical preparation, including identity verification, purity testing, potency measurements, sterility requirements, and acceptable impurity limits. Compliance with these standards serves as a cornerstone of quality assurance within both 503A and 503B compounding environments.

FDA Regulatory Action in 2023

In September 2023, the U.S. Food and Drug Administration placed nineteen peptide substances into Category 2 of the federal compounding substances list, indicating that the agency believed these compounds may present significant safety risks if compounded. Placement in this category effectively prohibited both 503A compounding pharmacies and 503B outsourcing facilities from preparing these peptides for patient use.

The peptides included in this regulatory action were AOD-9604, BPC-157, cathelicidin LL-37, CJC-1295, delta sleep-inducing peptide (DSIP), Epitalon, injectable GHK-Cu, GHRP-2, GHRP-6, ipamorelin, kisspeptin-10, KPV, Melanotan II, MOTS-c, PEG-MGF, Selank, Semax, thymosin-α1, and the thymosin-β4 fragment commonly known as TB-500.

The FDA identified three principal areas of concern in support of this decision. First, the agency cited the possibility that certain peptides could trigger immunogenic responses due to their biological structure and potential to stimulate immune recognition. Second, concerns were raised regarding impurities that might arise during peptide synthesis or degradation, particularly when manufacturing processes are not fully validated. Third, the agency noted that several of the peptides lacked what it considered sufficient clinical safety data in humans to support their routine compounding for therapeutic use.

Taken together, these concerns formed the basis for the agency's determination that the peptides should be placed into Category 2 pending further evaluation. The resulting policy action substantially altered the

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clinical landscape for physicians and patients who had previously relied on regulated compounding pharmacies to access peptide-based therapies.

Evidence Matrix: Human Safety Evidence for the 19 Peptides

Peptide	Level of Human Safety Evidence	Summary of Evidence
Thymosin-α1	Strong clinical evidence	Decades of clinical use for hepatitis, cancer, and immune disorders
Kisspeptin-10	Human clinical trials	Reproductive endocrine studies and sexual health research
AOD-9604	Multiple human trials	Randomized trials evaluating metabolic effects and safety
CJC-1295	Early clinical trials	Phase I studies in healthy volunteers
LL-37	Limited human studies	Clinical wound healing trials
Ipamorelin	Human exposure	Clinical studies in endocrine and GI contexts
GHRP-2	Clinical diagnostic use	Used in endocrine testing protocols
GHRP-6	Moderate evidence	Human GH stimulation research
GHK-Cu	Extensive topical safety	Cosmetic and wound-healing use
Semax	Human use literature	Russian neurocognitive research
Selank	Human use literature	Anxiety and neurocognitive clinical literature
BPC-157	Limited human evidence	Emerging pilot data; primarily preclinical
KPV	Mostly preclinical	Anti-inflammatory peptide research
PEG-MGF	Limited data	Muscle regeneration research
MOTS-c	Early clinical stage	Metabolic peptide under investigation
Epitalon	Early human reports	Longevity and telomere research
DSIP	Limited clinical evidence	Sleep and neuroregulatory research
TB-500 fragment	Limited data	Tissue repair research
Melanotan II	Documented adverse reports	Dermatologic peptide with safety concerns

Key observation: The evidence base varies dramatically, ranging from **well-studied clinical peptides to early research-stage molecules**.

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Global Peptide Manufacturing Supply Chain

An additional dimension influencing the regulatory discussion surrounding peptide therapeutics involves the geographic distribution of pharmaceutical ingredient manufacturing. Modern pharmaceutical supply chains are highly globalized, and the production of active pharmaceutical ingredients (APIs), including peptide precursors, occurs largely outside the United States. According to data published by the **U.S. Food and Drug Administration**, only a relatively small proportion of API manufacturing facilities supplying the U.S. market are located domestically.

Current estimates indicate that approximately nine percent of active pharmaceutical ingredient manufacturers serving the United States are based within the country. In contrast, a substantially larger share of API production occurs abroad. India accounts for roughly forty-four percent of global API manufacturing facilities supplying the U.S. market, while China represents approximately twenty-two percent. Europe contributes a significant additional share through established pharmaceutical manufacturing infrastructure across several countries.

This distribution illustrates the degree to which modern pharmaceutical development, and peptide manufacturing in particular, depends on international supply chains. As a result, the safety, consistency, and reliability of peptide therapeutics rely heavily on the integrity of upstream manufacturing practices and the transparency of global sourcing networks.

In practical terms, the quality of peptide-based medicines is closely linked to several critical factors. These include the chemical purity of raw peptide material, the traceability of manufacturing sources, and the regulatory oversight applied throughout the production process. Ensuring that peptide APIs meet appropriate pharmaceutical standards requires careful verification of synthesis methods, impurity profiles, and batch consistency.

Regulatory safeguards designed to address these concerns are already embedded within the compounding pharmacy framework. Facilities operating under **Current Good Manufacturing Practice (CGMP)** standards must implement validated manufacturing protocols, rigorous batch testing, and strict quality control procedures. In parallel, quality benchmarks established by the **United States Pharmacopeia** provide internationally recognized standards governing identity verification, purity thresholds, sterility requirements, and acceptable impurity levels for pharmaceutical substances.

Taken together, these regulatory mechanisms form the foundation of quality assurance for peptide-based therapies prepared within the United States compounding system. When properly implemented and enforced, they provide an important safeguard against contamination, manufacturing inconsistencies, and other risks that may arise within complex global pharmaceutical supply chains.

Policy Implications

The 2023 regulatory action by the **U.S. Food and Drug Administration** restricting nineteen peptides from compounding represents one of the most consequential interventions in the emerging field of peptide-based medicine. By placing these substances into Category 2, the agency effectively removed them from the therapeutic options available to physicians and patients through regulated compounding pharmacies. While the intention of this action was to address potential safety concerns and ensure appropriate regulatory oversight, the scientific record indicates that the evidentiary foundation supporting these peptides is far from uniform.

A growing body of literature demonstrates that several of the peptides included in the restriction possess substantial clinical safety data, documented human exposure, and in some cases decades of medical use in research or therapeutic settings. In addition, a number of these compounds continue to be investigated in active clinical research programs exploring applications in areas such as metabolic disease, neuroprotection, immunomodulation, and tissue repair. At the same time, other peptides within the same group remain earlier

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in the scientific development process and may appropriately require further investigation before broader clinical use can be justified.

This diversity in the depth and maturity of the evidence base raises an important policy consideration: a single regulatory classification applied uniformly across all nineteen peptides may not adequately reflect the scientific distinctions that exist among them. When compounds with established clinical exposure are regulated identically to those still in early investigational phases, the resulting framework may inadvertently restrict access to therapies that have meaningful scientific support while simultaneously failing to differentiate where more rigorous evaluation is warranted.

A more nuanced regulatory strategy, one that evaluates each peptide individually according to its safety profile, clinical evidence, and manufacturing quality, could provide a more balanced pathway forward. Such an approach would allow regulators to maintain high standards for patient safety while also preserving the ability of physicians and researchers to responsibly explore therapeutic innovation within the rapidly expanding field of peptide medicine.

Legislative Talking Points

1. The FDA's peptide restriction was overly broad.
The agency grouped together peptides with vastly different levels of scientific evidence.

2. Several peptides on the restriction list already have human clinical safety data.
Examples include Thymosin-α1, Kisspeptin-10, AOD-9604, and CJC-1295.

3. Compounding pharmacies already operate under strict regulatory standards.
503A and 503B facilities follow USP guidelines and CGMP requirements to ensure pharmaceutical quality.

4. The global pharmaceutical supply chain already requires rigorous oversight.
Most active pharmaceutical ingredients originate outside the United States, making regulatory quality standards essential regardless of drug category.

5. Physicians should retain the ability to prescribe emerging therapies when evidence supports safety.
Restricting compounding without clear evidence of harm may limit access to promising treatments.

6. A peptide-specific regulatory framework would better protect patients while supporting biomedical innovation.

Conclusion

Peptide therapeutics represent one of the most rapidly advancing domains within modern biomedical science, with expanding relevance across immunology, endocrinology, regenerative medicine, and neurobiology. These short chains of amino acids function as highly specific biological signaling molecules, capable of modulating cellular pathways with a degree of precision that has increasingly attracted the attention of clinicians and researchers seeking novel therapeutic strategies. As scientific understanding of peptide signaling continues to evolve, so too does recognition of their potential role in addressing complex clinical conditions that are inadequately managed by traditional pharmaceutical approaches.

The decision by the **U.S. Food and Drug Administration** in 2023 to place nineteen peptide substances into Category 2 of the federal compounding list was largely grounded in precautionary considerations, including theoretical concerns regarding immunogenicity, manufacturing impurities, and the perceived absence of sufficient human safety data. While the importance of regulatory vigilance in safeguarding public health cannot be overstated, the available scientific literature reveals a heterogeneous evidentiary

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landscape in which certain peptides possess meaningful clinical exposure and research support, whereas others remain earlier in the investigative continuum. The uniform application of regulatory restrictions across this diverse group has therefore generated debate within the scientific and medical communities regarding whether a more nuanced regulatory framework would better reflect the underlying evidence.

Within this context, a policy approach centered on **individualized peptide evaluation**, rather than broad categorical restriction, may offer a more balanced pathway forward. Such an approach would allow regulatory authorities to assess each peptide on the basis of its specific safety profile, clinical evidence, and therapeutic potential while maintaining rigorous standards for pharmaceutical quality and patient protection.

Current policy discussions within the Department of Health and Human Services, including statements made by **Robert F. Kennedy Jr.**, suggest that a reassessment of these classifications may be forthcoming. Should such a review occur, it presents an important opportunity to align regulatory policy with the evolving scientific landscape. A thoughtful reconsideration of peptide classification has the potential to reinforce patient safety while simultaneously preserving physician discretion and encouraging responsible biomedical innovation in the rapidly emerging field of peptide-based medicine.

Thank you HHS Sec. Robert F. Kennedy Jr.

Mark L. Gordon, MD

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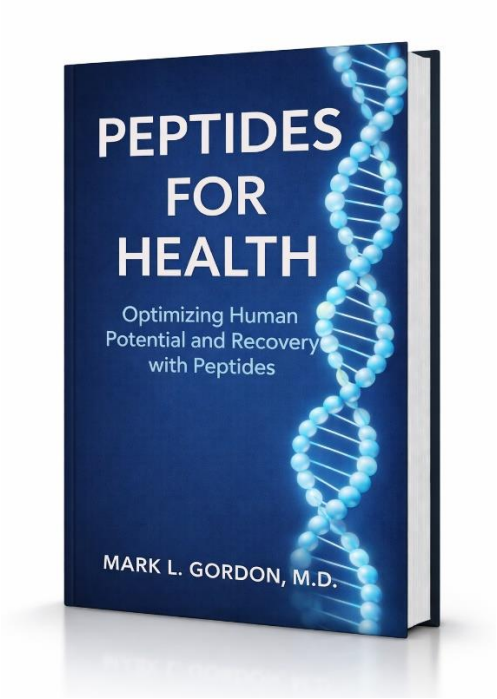

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