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# THE PEPTIDE CRAZE: THE SURGE IN USE OF OFF-LABEL AND NON-FDA AND FDA APPROVED PEPTIDES; IMPROVING SYNTHESIS

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**ABSTRACT**

The global peptide therapeutics market is undergoing a seismic shift, characterized by increasing demand for off-label and non-FDA and FDA approved peptides. While therapeutic peptides have established their position in the treatment of diseases like cancer, metabolic disorders and infectious diseases, the growing "peptide craze" is simultaneously being fueled by underground markets, fitness communities and direct-to-consumer platforms. This surge raises regulatory and safety concerns even as it pushes the industry toward innovation in synthesis technologies and sustainable practices. Technologies such as Resonant Acoustic Mixing (RAM), Inversion Mixing Technology Synthesizers (IMTS), Spin Rotating Technology Synthesizers (SRTS) and Shaking Technology Synthesizers (STS) are at the forefront of this transformation, significantly reducing environmental impact, process mass intensity (PMI) and hazardous solvent usage. This manuscript provides a comprehensive overview of the unregulated rise in peptide use alongside a scientific assessment of advanced and sustainable peptide synthesis technologies[1-10].

**KEYWORDS**

Off-label peptides, Non-FDA peptides, RAM, SPPS, Therapeutic peptides, Sustainability, PMI, PEI cycle time, IMTS. SRTS and STS.

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## INTRODUCTION

Peptides-short chains of amino acids-are increasingly sought after for their therapeutic promise. Their high specificity, reduced toxicity, and favorable pharmacokinetics make them ideal candidates for drug development. However, a parallel market has emerged: the widespread use of non-FDA approved and off-label peptides, ranging from cosmetic enhancements to performance boosters. These compounds are often sold online

without adequate clinical data or regulatory oversight.

Simultaneously, environmental concerns over the conventional Solid-Phase Peptide Synthesis (SPPS) process are prompting a shift toward greener synthesis pathways. Solvent-heavy SPPS not only drives up production costs but also yields a high environmental burden, with a PMI nearly 40 times that of small-molecule synthesis.

**The Unregulated Rise of Peptides**

Off-label peptide use is expanding rapidly, often promoted via social media and online forums. Compounds like BPC-157, TB-500, and CJC-1295 are marketed for wound healing, muscle growth, or anti-aging benefits, yet many lack rigorous clinical validation. This uncontrolled use poses significant risks-immunogenicity, off-target effects and manufacturing inconsistencies.

**Drivers of the Craze**

Perception of natural origin and safety

Easy online availability

Lack of stringent border checks

Desire for personalized or biohacked therapies

Despite the regulatory vacuum, this demand is catalyzing technological innovation in manufacturing, particularly in sustainable production.

**Innovation in Sustainable Peptide Synthesis**

Solid-Phase Peptide Synthesis (SPPS) remains the dominant method for assembling peptides. It provides high coupling efficiency but consumes massive quantities of toxic solvents like DMF and DCM, leading to filtration bottlenecks and reduced yields, especially for longer peptide chains. To mitigate SPPS shortcomings, several advanced synthesizers have been developed: Inversion Mixing Technology Synthesizer (IMTS): Uses orbital inversion to ensure uniform mixing, reducing dead zones and enhancing coupling efficiency.

Spin Rotating Technology Synthesizer (SRTS): Eliminates static resin problems by maintaining continuous rotation of resin beads, increasing homogeneity.

Shaking Technology Synthesizer (STS): Reduces exposure to oxidizing conditions by eliminating blade-based agitation.

Resonant Acoustic Mixing (RAM): RAM leverages low-frequency sound waves to agitate reactants, enabling enhanced penetration of reagents and reduced solvent use[1-10].

## RESULTS AND DISCUSSION

**Comparative Performance Analysis**

Table No.1 presents a side-by-side comparison of the automated SRTS and IMTS technologies versus manual batch mode synthesis. Notably, crude purity at Stage-II improved significantly (by ~20–25%) in both automated systems. Additionally, both technologies consistently demonstrated a time savings of 1-2 hours per amino acid coupling cycle and reduced filter aid handling during FMOC deprotection steps.

**Process Mass Intensity (PMI)**

Table No.2 outlines the process mass intensity of traditional manual batch mode versus modern automated technologies. A significant reduction in solvent and reagent usage was observed, contributing to improved sustainability metrics.

**Process Excellence Index – Cycle Time**

Table No.3 demonstrates the drastic improvement in cycle time, with automated synthesizers achieving up to 300% faster Fmoc coupling reactions and reducing total batch time by 70-75%.

**Process Excellence Index - Yield**

As shown in Table No.4, the yield of peptides synthesized using automated technologies showed significant improvement for both short and long sequences, ranging from 20% to 30% gains.

**Quantitative Analysis of Process Metrics**

Tables No.1-4 (see attached) compare traditional manual batch synthesis with the above-mentioned advanced methods in terms of:

**Stage-II Crude Purity:** Improved from ~50% to >85%

**PMI Reduction:** Solvent usage cut by >70%; material mass by >60%

**Cycle Time:** Amino acid coupling time reduced from 2-6 hours to 0.5-1 hour

**Yield:** Final product yield improved by 20-30%

**Impurities:** Total impurity count reduced by over 70%

**Environmental and Regulatory Implications**

While the unregulated use of peptides raises significant public health concerns, the shift to more sustainable synthesis is an encouraging trend. Manufacturers, under increasing pressure from environmental regulators and ESG standards, are adopting closed-loop systems and low-PMI technologies. Moreover, the adoption of green chemistry principles aligns with emerging regulatory frameworks, including the EU's REACH directive and India's push for green API manufacturing.

**Table No.1: Comparative Performance of Peptide Synthesizers**

| S.No | Parameter | SRTS | Manual Mode | Advantage (SRTS) | IMTS | Manual Mode | Advantage (IMTS) |
|---|---|---|---|---|---|---|---|
| 1 | Stage-II Crude Purity | ~80% | ~50% | ~25% higher purity | 65% | 45% | ~20% higher purity |
| 2 | Coupling Time | 0.5-1 hr | 2-6 hr | 1-2 hr saved | 0.5-1 hr | 2-6 hr | 1-2 hr saved |
| 3 | Filtration Time | 5-10 min | 0.5-1 hr | No filter aid replacement | 5-10 min | 0.5-1 hr | No filter aid replacement |
| 4 | Number of Impurities | 30 | 110 | Easier one-shot HPLC purification | 30 | 110 | Easier one-shot HPLC purification |
| 5 | Solvent Exposure | Minimal (closed loop) | High | Operator safety improved | Minimal | High | Operator safety improved |
| 6 | Oxidative/Degradation Impurities | <0.5% | >5% | Significantly reduced | <0.5% | >5% | Significantly reduced |
| 7 | Stage-III Yield | 0.5 w/w | 0.3 w/w | ~20% increase | 0.108 w/w | 0.075 w/w | ~30% increase |

**Table No.2: Process Mass Intensity Comparison**

| S.No | Parameter | Manual Batch Mode | Automated Synthesizers (IMTS/SRTS/STS) |
|---|---|---|---|
| 1 | Fmoc-AA molar ratio used | 3-6 moles (1.7kg) | Single-time use (0.85kg) |
| 2 | Total Solvent Consumption | 120kg | 30kg (PMI reduced by 90kg) |
| 3 | Total Mass Used | 90kg | 30kg (PMI reduced by 60kg) |
| 4 | Waste per Isolated Product | 90kg | 30kg (PMI reduced by 60kg) |

**Table No.3: Process Excellence Index - Cycle Time**

| S.No | Parameter | Manual Batch Mode | Automated Synthesizers |
|---|---|---|---|
| 1 | Coupling Reaction Time (per AA) | 2-6 hr | 0.5-1 hr (300% faster) |
| 2 | Total Cycle Time | 60-180 hrs | 15-30 hrs (reduced by 70-75%) |

**Table No.4: Process excellence index - yield**

| S.No | Product | Manual Batch Mode | Automated Synthesizers |
|---|---|---|---|
| 1 | 8 Amino Acid Peptide | 0.3 w/w | 0.5 w/w (~20% higher yield) |
| 2 | 29 Amino Acid Peptide | 0.07 w/w | 0.11 w/w (~30% higher yield) |

## CONCLUSION

The peptide therapeutics landscape is at a pivotal point. On one hand, the unregulated proliferation of non-FDA peptides calls for stricter oversight, global harmonization of peptide standards and greater public awareness. On the other, the technological innovations in synthesis-especially RAM, IMTS, SRTS and STS-are significantly improving environmental sustainability and economic scalability.

As global peptide use expands, especially beyond formal medical indications, the responsibility rests on researchers, manufacturers and regulators to ensure that safety, efficacy and sustainability are not compromised.

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## CONFLICT OF INTEREST

The author declares no conflict of interest.

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