Critical Testing Strategies for Autoinjector Drug Products

A Comprehensive Guide to Functional, E&L, CCIT, and Stability Testing in NIS-AUTO

White Paper

solvias

Executive Summary

As demand for self-administered therapies accelerates, autoinjectors, formally known as automated needle-based injection systems (NIS-AUTO), are playing an increasingly central role in modern medicine. These devices offer convenience, improve adherence, and support patient autonomy, while also easing the burden on healthcare systems. However, their dual role as both drug and device introduces a unique set of regulatory and performance challenges that must be addressed from early development through to commercialization.

Drawing from Solvias' deep expertise in combination product testing, this white paper outlines best practices and evolving regulatory expectations across four critical domains: functional testing, extractables and leachables (E&L), container closure integrity testing (CCIT), and stability testing.

By integrating these elements into a cohesive CMC testing strategy, developers can streamline timelines, minimize regulatory risk, and confidently bring safe, effective, and reliable autoinjector products to market.

Autoinjectors on the Rise:

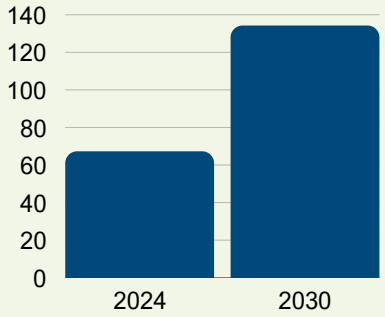
Opportunities and Risks in a Rapidly Expanding Market

Automated Needle-Based Injection Systems (NIS-AUTO), or autoinjectors, are medical devices designed for the self-administration of injections of a premeasured dose of a particular drug by patients and for easy administration by healthcare professionals in emergency situations.

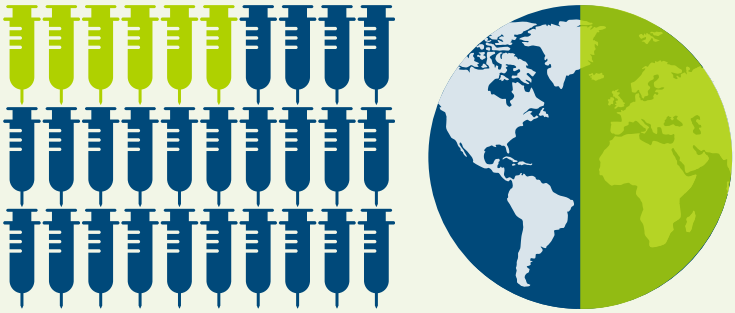
The autoinjector drug product market is estimated to reach USD 134.27 billion in 2030 from USD 67.30 billion in 2024, growing at a CAGR of 12.2%. In 2021, autoinjectors accounted for the delivery of six of the 30 top-selling drugs worldwide, representing approximately half of total global sales.

A significant contributor to this growth is the rising demand for Glucagon-like Peptide-1 (GLP-1) therapies. GLP-1 analogs, such as Ozempic®, Wegovi®, Rybelsus® and Mounjaro®, help regulate blood sugar and appetite, making them highly promising for treating both diabetes and obesity — conditions that impact over a billion people worldwide.

Self-administration supports patient independence and may reduce the burden on the healthcare system. However, device failures or use errors can have serious implications for patient outcomes, especially when these devices are used in emergency scenarios. Real-world examples underscore the importance of rigorous design verification, functional testing, and quality control. In 2023, Emerade® auto-injectors were recalled after reports that devices could fail to activate or activate prematurely if dropped, potentially preventing the delivery of life-saving epinephrine during an anaphylactic reaction. Similarly, EpiPen® auto-injectors were recalled following reports of activation failure due to a supplier component defect, which could delay or entirely block drug administration during a medical emergency. These incidents highlight the essential role of comprehensive testing to ensure the safety, efficacy, and trustworthiness of NIS products on the market.



The autoinjector drug product market: from $67.30 billion to $134.27 billion (CAGR:12.2%)



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High Concentration, High Complexity

Many autoinjector drug products on the market today are designed to deliver biologics, particularly monoclonal antibodies (mAbs) and peptides. These therapies are commonly prescribed for chronic conditions such as rheumatoid arthritis, diabetes, and obesity, and benefit greatly from autoinjector formats that enable convenient, self-administration outside of clinical settings. To further enhance patient convenience, manufacturers increasingly formulate these biologics at high concentrations, often exceeding 50 mg/mL. While this approach reduces injection volume and dosing frequency, it introduces challenges in formulation development, stability, and analytical testing. These challenges primarily stem from the following factors:

Increased Viscosity

High-concentration formulations often exhibit elevated viscosity, which complicates both manufacturing and analytical workflows. Handling such samples becomes more difficult, requiring careful pipetting, mixing, and injection into analytical instruments. High viscosity can also lead to inconsistent results and increased wear on equipment.

Elevated Risk of Aggregation and Self-Association

Proteins at high concentrations are more prone to aggregate, especially under stress conditions such as freezing. Aggregation can reduce product stability and therapeutic efficacy. If not detected accurately, aggregates can lead to underestimation of impurity levels and misinterpretation of product stability. Additionally, high concentrations can promote molecular self-association, potentially resulting in phase separation or gel formation, both of which compromise product quality.

Elevated Levels of Excipients and Buffers

To stabilize highly concentrated drug products, elevated levels of excipients and buffer components are often required. These compounds can interfere with analytical techniques such as mass spectrometry, capillary electrophoresis, and even simple UV absorbance measurements. As a result, samples may require additional pre-treatment, such as dilution or re-buffering. While sometimes necessary, such steps carry the risk of altering the sample's original state, potentially affecting the validity of analytical results.

In the following sections, we will examine the critical testing strategies required to ensure that autoinjectors perform safely, effectively, and reliably throughout their lifecycle.

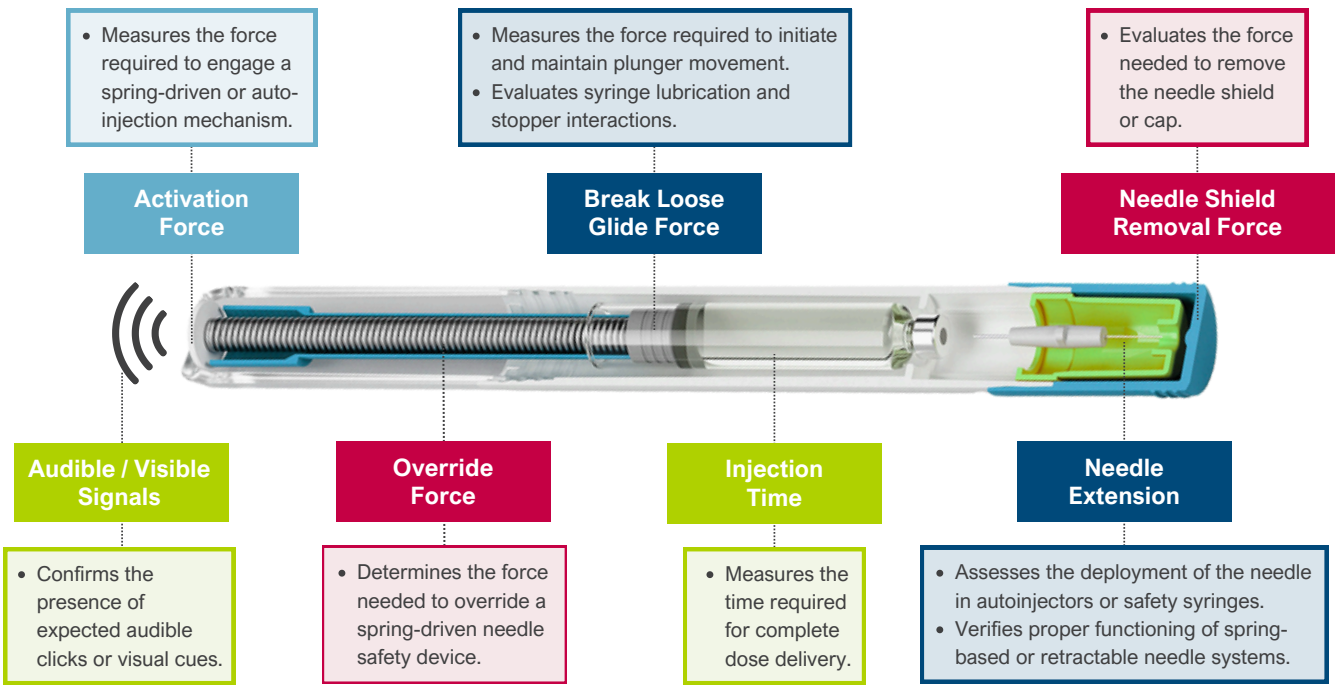
The Mechanics of Autoinjectors:

Functional Testing

Autoinjectors are typically powered by a pre-compressed spring that serves as the primary energy source. Upon activation, either by pressing the device against the skin or by triggering a button, the stored energy in the spring is released, driving a plunger forward. The resulting pressure propels the drug solution through the needle and into the patient's tissue. Most autoinjectors also have a secondary return spring, which counteract any residual force from the main spring to safely withdrawn the needle after injection is complete.

A delicate interplay of forces ensures that an autoinjector functions reliably. Injection performance depends not only on the spring force but also on glide and break-loose forces — the resistances encountered when initiating and maintaining plunger movement. Drug viscosity plays a key role in this dynamic: more viscous formulations — common in most biologics — require greater injection force. However, higher spring forces can generate a sudden pressure spike upon activation, placing significant stress on the device's components — stress that the system must be engineered to withstand. Additionally, thinner needles reduce injection pain and improve patient comfort, but they also increase flow resistance, further complicating the need for a finely tuned balance among all mechanical elements to ensure the device remains both effective and easy to use.

Thorough functional testing of autoinjectors is essential to ensure their safety, efficacy, and consistency to support successful regulatory submissions. This testing is primarily guided by ISO 11608-5:2022, which outlines a comprehensive framework for design verification, specifying the performance criteria required to demonstrate that the device reliably performs its intended function. As of July 2023, all parts of the ISO 11608 series are recognized by the FDA as consensus standards, making them highly relevant for pre-market authorization submissions in the United States. In Europe, adherence to these standards likewise supports regulatory approval by demonstrating compliance with industry best practices and promoting harmonization across the sector.



E&L Risks in Autoinjector Systems

Extractables and Leachables (E&L) studies are critical analyses conducted when developing a pharmaceutical product. These studies assess the potential for chemical compounds to migrate from containers, closures, and other packaging into the drug product. Therefore, E&L assessments are vital to ensure patient safety and consistent product quality.

Extractables are chemical substances that can be drawn out from packaging components, such as containers and closures, under laboratory conditions using solvents or stress conditions.

Leachables, on the other hand, are compounds that migrate into the drug product during its shelf life through direct or indirect contact with the packaging system.

Particularly for injectable drugs, which fall into the FDA's highest risk category, E&L testing plays a pivotal role in ensuring patient safety. For biologics, the presence of extractables and leachables can lead to protein aggregation, unfolding, and oxidation, thereby compromising shelf life and therapeutic efficacy.

Both extractables and leachables are regulated by global guidelines, yet none are entirely prescriptive. As such, E&L studies require a tailored, risk-based approach that aligns with the unique characteristics of each drug-product system.

Relevant regulatory references include:

- **USP <1663>:** Assessment of Extractables from pharmaceutical packaging and delivery systems
- **USP <1664>:** Evaluation of Leachables
- **USP <665>:** Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products
- **USP <659>:** Packaging and Storage Requirements
- **USP <381>:** Elastomeric Closure for Injections
- **USP <660>:** Glass Containers Used in Pharmaceutical Packaging/Delivery Systems
- **USP <661>:** Plastic Packaging Systems and Their Materials of Construction
- **ISO 10993-1:** Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process
- **ISO 10993-18:** Biological evaluation of medical devices - Part 18: Chemical characterization of medical device materials within a risk management process
- **ICH Q3E:** under development. Expected to be adopted by 2026.

Each E&L study is a complex forensic and analytical exercise, tailored to the specific drug and its packaging system. The goal is to identify and quantify all compounds of concern, trace their origin, and evaluate any associated toxicological risk. The results support critical decision-making during product development, either clearing the path for advancement or signaling the need for reformulation or packaging changes.

Sterility Assurance via CCIT

For parenteral drug products, maintaining sterility from manufacture through administration is a critical quality attribute (CQA). This requirement becomes particularly complex in the context of autoinjectors. In these systems, while the drug substance and drug product are manufactured under strict aseptic conditions, the secondary container (the autoinjector) is typically assembled in a non-aseptic environment. Components such as outer casings and activation mechanisms are integrated after the fill and finish process, increasing the risk of contamination if not properly controlled.

This is where Container Closure Integrity Testing (CCIT) plays a critical role. By confirming that the primary container system maintains a robust sterile barrier throughout handling, device assembly, and distribution, CCIT provides the necessary assurance that the drug product remains uncontaminated. Often referred to as "leak detection," CCIT encompasses a range of methods which are explored in greater detail in our white paper, *Container Closure Integrity Testing (CCIT): Ensuring Integrity, Compliance, and Safety.*

Regulatory expectations for CCIT are defined across several key guidance documents, including:

- United States Pharmacopeia (USP) <1207>
- European Union Good Manufacturing Practice (EU GMP) Annex 1
- Parenteral Drug Association (PDA) Technical Report 27
- International Council for Harmonisation (ICH) Q5C

Together, these frameworks underscore the importance of CCIT as a cornerstone of sterility assurance and regulatory compliance for parenteral products.

Access CCIT White Paper

Stability From Lab to Patient

As an autoinjector progresses through manufacturing, assembly, storage, shipment, and patient handling, the integrated drug product may be exposed to a variety of environmental stressors, including fluctuations in temperature, light, humidity, and mechanical agitation. These conditions can significantly impact the identity, purity, potency, and overall quality of the drug.

Autoinjectors are frequently used to deliver biopharmaceuticals, which are highly sensitive to degradation pathways such as denaturation, aggregation, deamidation, and oxidation. These molecules often require tightly controlled environmental conditions to preserve their structural integrity, biological activity, and clinical efficacy throughout the product lifecycle.

Stability testing is essential for identifying and quantifying physical or chemical changes that may occur in the drug product over time. These studies are designed to support the development of safe, effective, and reliable therapies by evaluating how a product behaves under various storage and handling conditions.

There are two primary types of stability studies:

Real-Time: The product is stored under its recommended storage conditions and monitored over time until it no longer meets predefined specifications. This provides direct evidence of the product's shelf life under typical use scenarios.

Accelerated: The product is subjected to elevated stress conditions, such as higher temperatures and humidity levels, to induce degradation more rapidly. By applying established kinetic models, this data helps predict the product's shelf life under normal conditions.

These studies inform critical decisions about storage and shipping requirements, shelf life, and labeling and handling instructions for healthcare providers and patients

Stability testing for biologics is governed by internationally harmonized guidelines, including:

- **ICH Q1A(R2):** Stability Testing of New Drug Substances and Products
- **ICH Q5C:** Quality of Biotechnological Products – Stability Testing of Biotechnological/Biological Products

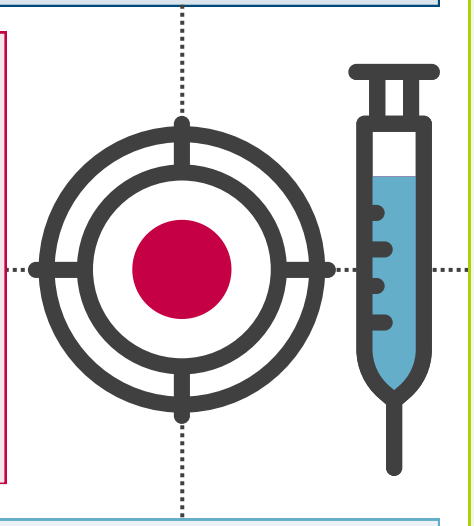
An Integrated Approach to Autoinjector Testing

A common pitfall in autoinjector development is treating device testing as a standalone effort, disconnected from the overall CMC testing strategy. This siloed approach can delay the identification of critical issues. When critical issues are only identified in later stages of development, remediation is more costly and time-consuming.

At Solvias, we understand that autoinjector performance is not defined solely by mechanical precision of the device or the quality of the drug in isolation, but by the complex interplay between the two under real-world conditions. We support developers at every stage with services tailored to the unique challenges of drug–device combination products:

Drug–Device Compatibility Studies: Our assessments simulate real-use conditions, ensuring mechanical performance and formulation behavior are aligned. These studies are strategically tied to CMC timelines to prevent delays.

Stability Studies Under Real and Accelerated Conditions: From early formulation screening to final product shelf-life evaluation, our ICH-compliant stability programs detect and characterize degradation pathways critical to product safety and efficacy.



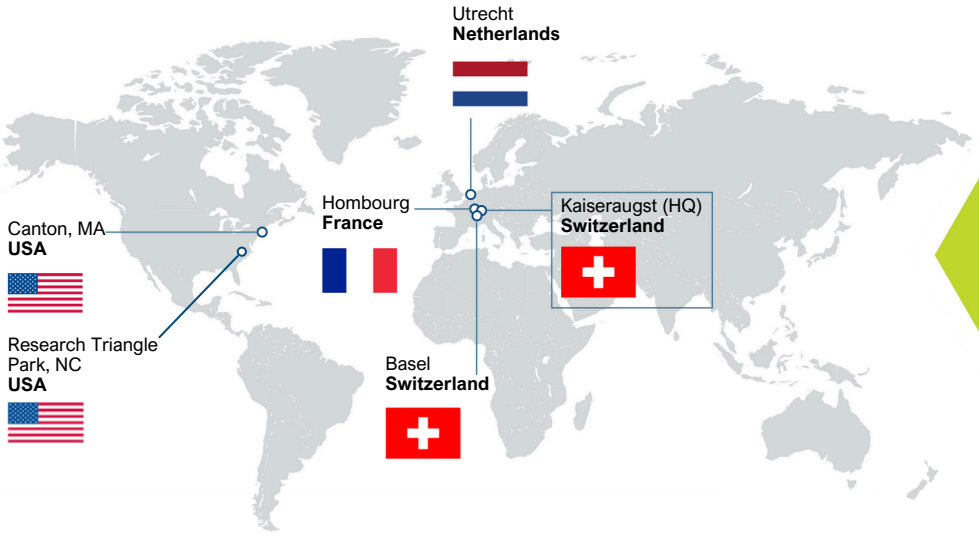
Full ISO 11608 Series Compliance: We offer end-to-end testing that meets the requirements of the entire ISO 11608 standard, recognized by the FDA and other global regulatory authorities, ensuring robust design verification and accelerated regulatory acceptance.

Container Closure Integrity and E&L Testing: Our experts combine CCIT and extractables and leachables analyses with formulation-specific insights. With years of experience and extensive regulatory knowledge, we avoid common pitfalls and successfully manage highly complex studies. With our technology and expertise, we can identify and quantify compounds with extreme sensitivity, enabling us to reach even the most challenging analytical evaluation thresholds (AETs).

By integrating these key services under one roof, Solvias enables a seamless and scientifically rigorous pathway from development to market. Our collaborative approach, regulatory expertise, and breadth of capabilities empower developers to mitigate risk, streamline development, and deliver safer, more effective autoinjector products. For further information, contact us at **info@solvias.com**.

Why partner with us?

- CDMO/CRO
- Founded in 1999
- 800+ team members
- 175+ PhD-level scientists
- GMP, GLP, ISO9001 certified
- 22.5K sqm of lab capacity
- 700+ customers worldwide
- 6 centers of excellence



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