ISO 11608 Changes to Mechanical Injector Requirements and Device Verification

CAMBRIDGE DESIGN PARTNERSHIP

A revised and updated standard

Patients receive over 16 billion injections annually. With most new therapies arriving on the market in a parenteral presentation, ensuring injections are safe and effective has never been more critical. Since the publication of ISO 11608-1: Pen Injectors for Medical Use – Requirements and Test Methods in 2000, the 11608 series of standards have set the benchmark for the design and verification of needle-based injection devices.

The 11608 series of standards come under the remit of ISO Technical Committee 84 (ISO TC84), a committee focused on defining the requirements and test methods to ensure safe and effective devices are made available to the greatest number of people. The scope of the standard has increased significantly since ISO 11608-1 was first published, but the staggered publication of the different sections led to inconsistencies, and new device innovations were no longer adequately described by the existing guidance.

An ambition to align the different parts of the standard, offer better guidance to device developers, and reflect advancements in the design of injection systems has led to a fundamental review of the various parts of the standard. This revision of the standard was published in April 2022 and represents the most fundamental rewriting of the standard since it was first published. The new ISO 11608 series of standards is now comprised of seven separate documents:

Part 1: Needle-based injection systems – requirements and test methods
Part 2: Double-ended pen needles
Part 3: Containers and integrated fluid paths
Part 4: Needle-based injection systems containing electronics
Part 5: Automated functions
Part 6: On-body delivery systems
Part 7: Accessibility for persons with visual impairment

This revision introduced a new classification of needle-based injector, the on-body delivery system (OBDS) described in Part 6 of the standard. (Part 7 was not updated in this revision, as the standard was first published in 2016, and a review in 2021 did not identify any cause for revising the standard.)

Notable changes by section

As most needle-based injectors (NIS) are built around mechanical systems, I will focus on the changes that designers and manufacturers of mechanical NIS should be aware of and the implications of these changes for device verification. This means I will concentrate on Parts 1, 2, 3, 5, and 6. This document should not be considered a substitute for the updated standards – but I believe it will be helpful to device developers and manufacturers approaching the updated content.

ISO 11608-1 – Needle-based injection systems – requirements and test methods

This latest version of the standard established Part 1 as the fundamental parent component of the standard. The document describes Part 1 as the 'horizontal' standard, so far as the principles and test methods apply to all NIS. The document maps out the relationship to the other parts of the standard and gives guidance on when they should be applied. This section also introduces the concept of OBDS, more fully described in ISO 11608-6. The introduction also stresses the nature of NIS as combination products and the importance of understanding how the different medicinal products in NIS can affect and define the behavior of the whole system.

In addition to providing general guidance on the application of the whole of ISO 11608, this new revision of Part 1 introduces several new concepts to the series. The most important new concept is Primary Function. The Primary Function of the NIS is a function that, should it fail to perform, would result in failure to deliver the medicinal product via the correct route accurately. Any device failure that would lead to unacceptable harm to the patient would also be classed as a Primary Function. Dose accuracy is always a Primary Function.

Part 1 also introduces the concept of Functional Stability, which describes the ability of the NIS to maintain its Primary Function over a specified period and/or number of actuations (in the case of multi-dose NIS). If the number of uses of a NIS can't be restricted in the design of the device, it must be tested to 1.5x the expected life.

The test sample quantities have been revised and updated (Table 3 – Test Case Matrix), and the relationship between the different device classifications and test cases has been made much clearer. Cool and warm atmospheric testing (11608-1:10.2) can now be conducted under standard laboratory environments, provided that the time between removal from a test chamber and testing of the device is minimized and justified. In other words, you would need to remove one device at a time from the environmental chamber and test the NIS immediately. Regarding pre-conditioning, devices are now expected to be tested after simulated (or actual) transport pre-conditioning and when appropriately aged. However, there is no expectation that these test pre-conditions should be combined, or 'stacked' (11608-1:10.2.3).

There are also several smaller modifications to ISO 11608, including moving all electronics and EMC testing requirements to ISO 11608-4, adding a choking hazard warning for small components, and the associated test fixture. A section has also been added to the document giving guidance on design verification with reference to ISO 13485. The lighting conditions for visual inspection have been updated so that inspection for damage must be conducted in a bright environment (750 lux or more), and visual markings must be legible in low light (100 lux or less).

ISO 11608-2 – Double-ended pen needles

The changes to ISO 11608-2 are more subtle, including the change in the title of the standard from 'Needles' in 2012 to 'Double-ended pen needles' in 2022. This change made it clear to the reader that this section of the standard focuses on the specification and testing of double-ended needles for cartridge-based NIS.

The determination of flow rate has been expanded to include suggested flow ranges, and the sample sizes have been brought in line with the requirements in ISO 11608-1. The testing requirements to confirm compatibility between a needle and a specific NIS have been revised to include dose delivery and needle hub removal force. In addition, the samples needed for functional compatibility have been reduced, and guidance has been added on the requirements for the inner needle shield.

ISO 11608-3 – Containers and integrated fluid paths

The scope of ISO11608-3 has now been expanded beyond defining cartridge geometry and performance to cover NIS containers and integrated fluid paths. This change has been prompted by the development of OBDS devices, where the connection between the primary container for the drug product and the injection site has become far more complex than a staked or double-ended needle.

The requirement for resealing the cartridge has been reduced from 1.5x the intended use to a minimum of 1.0x the intended life. At the same time, the particle size for coring characterization has increased from 50um to 150um or larger. General requirements for soft cannulas and fluid line connections have also been added, with the reader directed to ISO 10555 for soft cannula requirements and ISO 7864 for steel cannulas. Cartridge geometry definition has also been moved to an informative annex, meaning it's no longer mandatory.

ISO 11608-5 – Automated functions

The revised text for ISO 11608-5 now directs the reader to ISO 11608-1 for many general requirements, focusing on automated needle insertion and dose delivery. The dose accuracy test for automated needle insertion has been changed slightly to ensure that only medicinal product delivered to the minimum specified injection depth is used for verification testing.

Requirements for fenestrated needles (needles with holes in the side) have been defined, the implications of non-perpendicular needle and cannula insertion explored, and measurement methods defined. The dose accuracy test has been changed for needles with automated insertion, and defining and measuring automated dose delivery time is now a requirement.

ISO 11608-6 – On-body delivery systems

As stated in the introduction, April 2022 marked the first publication of Part 6 and the introduction of the OBDS device class. The crucial difference between an OBDS and an infusion pump is that the OBDS's performance is defined by dose accuracy for a fixed volume; an infusion pump is defined by the rate at which the medicinal product is delivered.

OBDS are also distinct from other NIS types in that they are attached to the body, while traditional NIS are held by the user for the delivery duration. The attachment to the body may be due to extended delivery times or driven by the intention to apply an injection to the body after a predetermined delay, such as following a surgical procedure or chemotherapy.

The requirements and design guidance reflect this difference in use, and the concept of a delivery profile (as a characterization tool, not a performance requirement) has been included to help device builders better understand their products. This part of the standard also includes the addition of guidance in selecting and verifying adhesive attachment methods to ensure that the OBDS will be held securely without causing tissue trauma on removal.

The extended delivery and wear time of OBDS also mean that they are subject to stresses that other NIS are not. This includes the effects of having to work in different orientations, exposure to different operating temperatures, and the influence of shock and vibration during delivery. As OBDS are often targeted at highly viscous drugs, such as biologics, the impact of temperature and movement during delivery should be understood and verified.

Understanding the impact

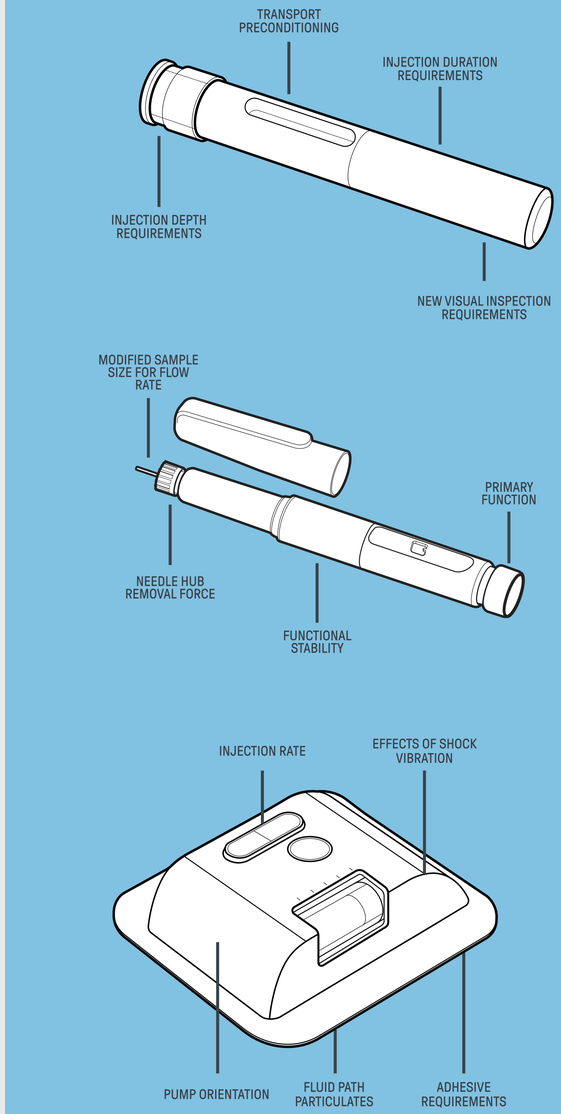
What steps should you take if you are currently developing an NIS or OBDS that falls into the variety of devices covered by the latest version of ISO 11608? Medical device developments, particularly for combination products, take multiple years. In recognition of these development timelines, all parts of ISO 11608 point to ISO/TR 19244 for guidance on when to implement these changes.

If the device is already on the market, and there is sufficient evidence to show that the device is safe and effective, there is no need to demonstrate compliance with the new standard.

If the device is not on the market, there is a period of no more than three years from the time of publication of the new standard to claim compliance by reference to the previous version of the standard. The only exception to this guidance would be in the case of a marketed device that needs to undergo a substantial redesign after the three-year grace period. Use established risk assessment techniques to identify if the design change planned is significant enough to require re-verification of the product.

If your device is not on the market and it is likely to be submitted to a regulatory authority more than three years after the publication of the new standard, the device should be verified to the latest version of the standard. It should also be noted that manufacturers can reference the new standard immediately, should they wish to. There is scope within the standard (11608-1:5.3) to modify requirements, specifications, or test methods, provided these deviations are documented and justified through a robust risk-based approach.

Manufacturers in the early stages of a development program should update device requirements and verification plans to address the new content in ISO 11608.



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