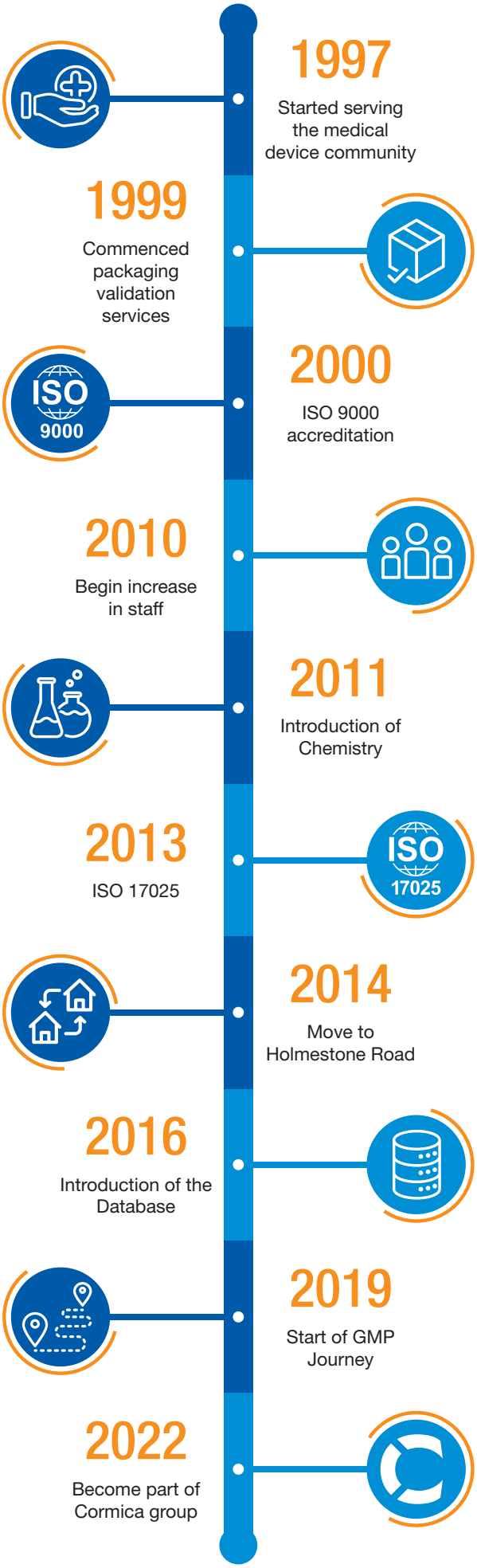
MEDICAL ENGINEERING TECHNOLOGIES

A CORMICA® Lab

Guidebook to Combination Device Validation and Verification

Volume 2

Contents



About MET

Medical Engineering Technologies Ltd was founded in 1997 by Mark Turner, a former perfusionist with a passion for saving lives by improving medical devices. Following rapid growth in the business, Turner grew the company into what it is today - a thriving medical device test house, with expertise in medical device testing across Combination Devices, Physical Devices, Chemistry, Distribution and Packaging.

MET was acquired in 2022 to become part of the Cormica group, along with Wickham Micro, in order to further improve and increase the scope of testing, which in turn has created a fully comprehensive resource for medical device developers.

MET Services

At MET you can choose from a variety of ISO 17025 accredited services, including:

- Transit and Packaging Validation
- Real Time & Accelerated Ageing
- Batch Release Testing
- Physical Device Testing including Catheters, Small Bores, Infusion Sets
- PFS & AI Testing according to ISO 11608, ISO 11040 and ISO 7886
- Chemistry Testing including Chemical Characterisation, Extractables & Leachables, Degradation Studies, Particulate Contamination, TRAs
- Biological Evaluation Plans and Reports (BEPs/BERs)
- Human Factors Services
- Combination Devices
- Physical Devices
- Transit & Packaging
- Chemistry

About Cormica

We are committed to advancing patient care through exceptional testing solutions for medical device and pharmaceutical manufacturers. Our partner laboratories, Wickham Micro Ltd and Medical Engineering Technologies Ltd, operate under stringent GMP, GLP, and ISO 17025 standards to provide you with reliable, high-quality testing services. Through our comprehensive range of offerings, we enable our clients to launch and release their life-saving products to more markets globally, both quickly and safely.

Cormica's Testing Services

- Analytical Chemistry
- Biocompatibility & Toxicology
- Microbiology, Sterility & Environmental
- Functional and Performance Testing
- Packaging, Seal & Transit Testing

Cormica's mission is to improve patients' lives by providing comprehensive testing services, enabling clients to launch and release their products safely and rapidly across the world.

The Project Process: From Enquiry to Test Report

Enquiry

Once an enquiry comes into MET, a member of the sales team is assigned.

If a client is new, a **New Client Form** and **Mutual NDA** are sent in order to ensure all details are accurate and confidential.

Questionnaires are sent to obtain details of the testing, samples, time frames and type(s) of projects required.

A **Quotation** is produced, sent to the client and any required revisions are carried out.

MET receive a **Purchase Order** from the client, reflecting the project reference number, title and cost.

A **Sample Submission Form** and **Order Acknowledgement** are sent to the client to confirm that the project is active, and the project is handed over to the technical team.

Samples

Samples can be sent to MET at any point following client receipt of the Sample Submission Form, which is to be sent with the samples.

Once samples are received, MET will supply a **Sample Receipt**, including a sample receipt number, sample details for testing and a report date.

The **Invoice** for the project will be sent via MET's accounts department.

Test Protocol

A draft Test Protocol is created, including:

- Client details
- Sample details
- Design of the project
- Test methods
- Acceptance criteria.

The **Test Protocol** may be changed/revised by the client e.g. specific batch numbers added.

The Test Protocol is signed by the client.

Testing begins.

Testing

Samples are labelled and in-house datasheets are created.

Testing is carried out according to the **Test Protocol**.

Technicians and project managers keep the client updated on the progress of the project.

Should there be any **Out of Specification** results or other issues, testing is halted, and the client is immediately informed in order to decide how they wish to continue.

Reporting

Raw data is checked by Quality Assurance to ensure compliance to internal procedures.

Expanded uncertainty and decision rule is applied to test data (if applicable).

A **Test Report** is created including:

- Client details
- Deviations from the protocol
- Technicians involved
- Summary of data
- Discussion
- Appendix of raw data

The Test Report is reviewed by Quality Assurance and sent to the client.

Document Trail

New Client Form & Mutual NDA

Quotation

Purchase Order

Order Acknowledgement & Sample Submission Form

Sample Receipt & Invoice

Test Protocol

Test Data/OOS Documentation

Test Report

Laboratory Capabilities

Introduction

An educated preclinical partner/test facility, such as MET, can provide regulatory guidance to help assist in getting a product to the marketplace. The process of addressing these requirements can be planned to ensure efficient project management and help reduce costs.

MET's Knowledge Basis

MET is accredited under ISO 17025, which verifies MET's approach to staff training, sample handling, equipment and method creation. This accreditation allows MET to own an extensive list of standards which are turned into internal Work Instructions. These standards include:

ASTM D4169

Standard Practice for Performance Testing of Shipping Containers and Systems

ISO 11607

Packaging for Terminally Sterilised Medical Devices

ASTM F1980

Standard Guide for Accelerated Aging of Sterile Barrier Systems and Medical Devices

ISO 18562

Biocompatibility Evaluation of Breathing Gas Pathways in Healthcare Applications

ISO 10993

Biological evaluation of medical devices

ISO 11608

Needle Based Injection Systems for Medical Use (Requirements & Test Methods)

ISO 11040

Pre-Filled Syringes

ISO 7886

Sterile Hypodermic Syringes for Single Use

ISO 80369

Small-bore connectors for liquids and gases in healthcare applications

To further improve MET's source of information, a Subject Matter Expert (SME) programme is in place with fields of expertise in ISO 11608, Transit & Packaging Validation, Tubing/Catheters, as well as employees being part of standards committees.

Equipment

MET have a comprehensive list of calibrated equipment, including Mecmesin Test Stands, Zwick Roell, Profile Projectors, HPLC, GC-MS, 4 Place Balances, Vibration Machine, Burst Tester, creating an endless list of possible tests.

MET Project Types

Method Development

If a test has not been carried out before, either at all or in conjunction with a specific product, method development is required in order to create a test that is usable for its intended purpose. Method Development projects proceed as follows, as a first step for a new project:

1	Method Development Protocol	Specifies the test(s) to be developed, the correlating standard(s) and how many samples are required
2	Method Development Testing	Testing is carried out to assess the method with test rigs to develop a method which will be suitable for the required outcome
3	Method Development Report	Details the method to be used in testing, as well as the test results

Method Validation

Test methods are validated on a product-to-product basis, often following Method Development should MET not have an existing method. There are multiple variations of how Validation can be carried out, but generally, three technicians test 10 samples each on three occasions, and the GRR (Gauge Repeatability and Reproducibility) results are statistically analysed. Method Validation projects proceed as follows:

1	Method Validation Protocol	Details the test(s) to be validated, how many samples are to be tested, the design of technicians/ occasions and validation acceptance criteria
2	Method Validation Testing	Testing is carried out
3	Method Validation Report	Test results are summarised and reported, confirming conformance to validation acceptance criteria

Batch Release

A contract is set up in order to establish the cost and frequency of a batch of samples, as well as a protocol which testing will be carried out in accordance with. MET have a testing schedule to ensure that the batch release testing is not interrupted by other projects and technicians are aware of when to expect samples.

Stability Testing (ICH (Q1A) Guidelines)/Shelf Life Studies

Based upon the required shelf life of the product, a stability testing programme will be established in order to assess the product's conformability with the standard throughout its life. This may involve testing multiple time points, for example, 1 Month, 6 Months, 1 Year, 2 Years, or one timepoint at the end of the shelf life. A control (i.e. un-aged) group will be tested at Time 0 in order to have comparative test results.

Investigative/Bespoke Projects

There is the possibility that some testing may not be required for a submission, but clients want to discover something about their product which they would not get from routine testing. In this case, MET work with clients to find a way to obtain the information/data that is required to reach the desired outcome.

Devices & Standards

1. PFS – ISO 11040 (4-8)

A prefilled syringe (PFS) is a cylindrical pump, composed with a plunger on one end and a nozzle at the other, containing an active pharmaceutical ingredient within the barrel. Pre-filled syringes are dominating the drug delivery market, due to ease of use for patient care and the accuracy of the dose.

For these reasons, the global prefilled syringes market is projected to grow from $5.62 billion in 2020 to $15.73 billion by 2030, at a CAGR of 10.8% in forecast period 2021-2028.

This, however, doesn't mitigate the need to initially ensure the design of the device does not impact the functionality or dose accuracy, which is why compliance to relevant standards is necessary.

One such standard for PFS is ISO 11040. This testing standard addresses the design and functional properties of the prefilled syringes. Laboratories that manufacture syringes must follow 21 CFR Part 11, which is why MET work to the principles of CFR Part 11.

ISO 11040 is composed of 8 parts:

Parts 1-3 refers to the subcomponents of cartridges used for local anaesthetic in dental settings.

Parts 4-6 refers to the subcomponents of prefilled syringes including glass barrels, plastic barrels, and plunger stoppers.

Part 7 refers to the packaging systems.

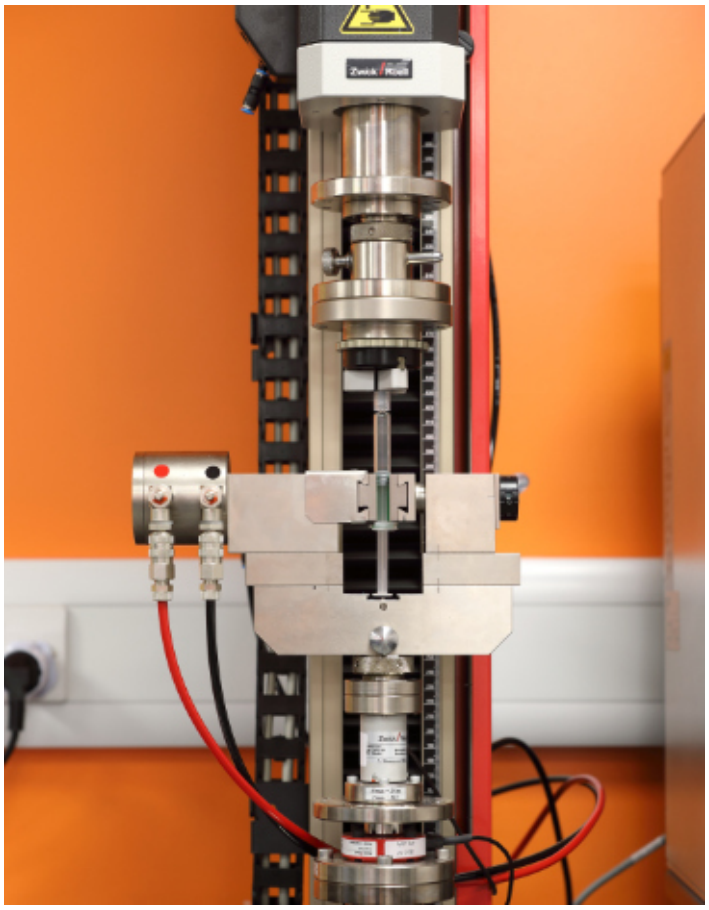
Part 8 refers to the test methods and evaluation criteria for the finished syringe rather than the individual subcomponents.

Additional standards may include; ISO 80369-20 and ISO 7886-1, USP 1207, ISO 23908:2011 (EN ISO 23908:2013).

ISO 11040 provides a number of tests to be considered:

- Dimensions- syringe inner and outer diameter
- Functional testing of Luer connection with reference fittings
- Flange – Breakage Resistance
- Plunger – Break Loose
- Luer Cone – Breakage resistance
- Barrel – lubrication gliding test force, safety activation force.
- Needles or syringes with Staked Needle – Penetration force, dimensions, design, lubrication, and pull out/off force/removal
- Closure system – liquid leakage resistance
- Luer Lock Adaptor Collar – Torque resistance, pull out force
- Luer lock rigid tip cap - Unscrewing torque
- Needle Shield - Cap Removal or pull-off force
- Container closure integrity – dye solution tightness, hydrogen, liquid leakage test.

When MET are approached with the needs and requirements of a product, the expert team of technicians and salespersons will direct and advise as to how the testing will be carried out. The available machinery is versatile, therefore it can be adapted to develop a method accordingly. MET are highly familiar with carrying out studies such as: gauge repeatability and reproducibility, design verification, marketing pack and functional stability on pre-filled syringes.



Scan the QR code see our pre-filled syringe testing services

2. Auto Injectors - ISO 11608 -1 and -5

Advancement in combination devices such as PFS have led to auto injectors, an easy-to-use delivery system, designed especially for patients and untrained personnel to administrate the measured dose(s).

An autoinjector consists of a cartridge or pre-filled syringe, medication or placebo, attached to a mechanical mechanism (device housing). Regulations must be applied on the drug and the cartridge/prefilled syringe, however, in addition, further regulations must be applied to the above components when attached together, which is why auto injectors are defined as combination products and the merging of these components can cause obstacles for manufacturers.

MET respect that meeting timelines for submissions is vital to preventing bottlenecks in the manufacturing process. Although quality and practicability are key, it will be ensured that production isn't any longer than necessary.

In the main, two types of automated needle injection systems are prevalent:

Auto Injectors require pressure to activate the needle shield, which in turn will activate the spring system, which will activate the needle and drive the drug product out of the device and into the patient. As this process requires little to no human control, it is classified as an automated system and its quick and easy use makes this design more effective for anaphylactic reactions, when the administrator may not necessarily be a healthcare professional or the patient, but even untrained personnel can quickly know what to do.

Pens have a push button. These types of NIS require a person to push down onto the system's designed button in order for the spring system to be engaged and the drug product to be expelled via the needle. This can be done once the dose size is set by the user if the device is a variable C type. Hence why this design suits patients with autoimmune diseases or diseases that require patients to be medicated on a regular basis.

ISO 11608-1 and -5 are the most commonly used international standard to be applied to auto injectors and pens, to test for efficacy and to achieve 95% confidence on the acceptance of the primary functions of these devices.

Due to differences in the designs of NIS, NIS are categorised into 6 different system designations. These will aid in identifying which test methods for dose accuracy should be assigned to the device. Table 1 describes the differences between the system designations.

Table 1 – System Designations

	Multi-Dose Container	Single-Dose Container
NIS with replaceable container	**A:** Each container holds multiple doses, the size of which may be fixed or variable (set by the user)	**B1:** Each container holds a single dose, and the entire deliverable dose is expelled.
		B2: The container holds a single dose, and a portion of the deliverable volume is expelled.
NIS with non-replaceable container, which is integrated, or user assembled	**C:** The container holds multiple doses, the size of which may be fixed or variable (set by the user)	**D1:** The container holds a single dose, and the entire deliverable volume is expelled.
		D2: The container holds a single dose, and a portion of the deliverable volume is expelled.

The assembled NIS (without a needle) will undergo conditioning prior to testing. Conditioning will be specified by the client and can be any of the following (Table 2).

Table 2 – Pre-Conditioning

Condition	Chamber Conditioning					Stress Conditioning	
	Cool	Standard	Warm	Dry Heat	Cold Storage	Free-Fall	Vibration
Temperature (°C)	5 ± 3	23 ± 5	40 ± 2	70 ± 2	-40 ± 3	N/A	23 ± 5
Humidity (% RH)	N/A	50 ± 25	50 ± 10	50 ± 10	N/A	N/A	50 ± 25
Time Spent in Conditioning	> 4 hours	> 4 hours	> 4 hours	> 96 hours	> 96 hours	N/A	N/A

ISO 11608 provides a number of tests to be considered:

Actuation Force – Automated function is activated and measurements such as the torque to rotate the safety lock or force to operate the button are recorded. This test provides information as to whether or not the NIS could inadvertently be actuated or triggered and if a subsequent actuation could inadvertently occur, without an explicit user-initiated step.

Needle Inspection – The needle is visually inspected at a specific magnification and environmental lighting conditions and no obvious damage, kinking or bent lumens should be seen for the requirements to be met.

Needle Extension Length – The NIS is operated as intended, however, using a 3D printed device, the needle is prevented from retracting back into the needle-hiding feature. Using optical machinery, the needle length is then measured from the tip end to the hub of the device. This test determines whether or not the device delivers the product at the intended injection depth.

NIS Dose Accuracy Testing – Type C and D – The difference between the intended dose and the actual dose; This is generally measured gravimetrically and plays a critical role in patient safety and drug product efficacy.

Injection Delivery Time – Whether too long or too quick, the result could cause unnecessary pain and harm to the patient and ,potentially, an incomplete dose. Using the "manufacturers" specified and justified time frame, based on human factors and/or engineering studies, it can be determined if the injection time is within the acceptable limits.

Safety Override Force – Tests whether the needle could remain exposed and become a biohazard as well as a sharps hazard, therefore aids in the safety of others as well as the administrator.

Cap Detachment Force – Considered a primary function, as any delays in removing the cap will delay treatment. On the other hand, if the cap removal force is low, the risk of it being removed unknowingly could induce cross contamination. Both cases could cause unacceptable harm to the patient.

3. OBDS

On-Body Delivery Systems (OBDS), also known as Wearable Injectors, have been around for many years and are more recently becoming more common. OBDS are wearable delivery devices capable of delivering high volumes of medication and / or those with high viscosities, all while providing ease and comfort to the patient.

These devices generally attach to the patient via a sticky patch and the dose is delivered via either a needle or a soft cannula. An advantage to OBDS is that it eliminates some of the risks that are associated with traditional delivery systems (Pre-Filled Pens & Pre-Filled Syringes).

With the recent release of ISO 11608-6:2022 Needle-based injection systems for medical use – Requirements and test methods – Part 6: On-body delivery systems, we now know the conditioning and testing requirements for OBDS.

Potential conditions include but are not limited to:

- Temperature
- Humidity
- Vibration
- Orientation

Tests methods include:

- Adhesion
- Dose Accuracy (including delivery time)

  Needle / Cannula Displacement

There are various test methods that can evaluate the performance of the adhesion: Tack, Peel and Shear. For pressure sensitive adhesives, the Tack test is most relevant and it is the measure of how quickly the bond is formed between the adhesive and the patient. The Peel test measures the force needed to detach the adhesive from its intended surface. For the Shear test, the time is measured to remove a vertically-mounted sample from its intended surface.

For Dose Accuracy, there are three characteristics that are relevant: Dose Accuracy, Dose Delivery Time and Dose Delivery Profile.

Knowing the positioning and placement of the needle or cannula on the patient during dose delivery is highly important

and the patient should not adversely affect the needle or cannula position. The requirements for the placement of the needle or cannula should reflect the intended tissue and duration of the dose delivery. Other hazards that are likely to need addressing include movement, adhesive strength and adhesion, and damage during insertion.

As per the other various parts of the ISO 11608 series, the device manufacturers have input into aspects of testing for their specific device. For example, the manufacturer shall determine the temperature range of the OBDS during drug delivery. This is due to body temperature potentially having an impact; an OBDS that has an extended dose delivery time may warm the device while affixed to the body.

4. Cartridges – 11608-2

Cartridges are containers holding a medicinal product that is closed on one end with a cartridge cap and disc, and on the other end with a plunger stopper.

The revised version of the ISO 11608-3 includes information regarding integrated fluid paths and NIS containers, as well as cartridge geometry and performance. The cause of these changes is the OBDS (On-Body Delivery Systems); read the OBDS section above for more information on OBDS.

It is important to note some of the modifications include general requirements for fluid line connections and soft cannulas. MET is prepared to meet these requirements.

MET cover all ISO 11608-3 tests including:

- Plunger Force
- Leakage
- Dimensions – length, overall diameter and plunger insertion depth
- Eccentricity
- Meniscus
- Resealability
- Coring
- Needle Bond Strength

Some examples of the process and requirements for such testing are:

Fragmentation testing: When a needle or similar type access point pierces a cartridge or reservoir of a NIS, visible elastomeric particles can be formed. Fragmentation testing requires piercing the cartridge the number of times specified in ISO 11608-3 and emptying the contents onto a 5µm filter to see the number of particles. Coring involves purging the needle/access device onto a filter. Fragmentation, in conjunction with coring testing, is required to assess that the particles do not interfere with correct dosage.

Needle bond strength testing: required when a rigid cannula is part of the fluid path of a cartridge or reservoir. A minimum force is defined that will pull the rigid/tapered or needle/soft cannula/introducer needle and test the strength of the union between the needle and its connection point to the NIS and ensure it remains affixed.

Eccentricity: A digital dial gauge is used simultaneously with a torque device to rotate the sample 360°. The maximum runout is indicated for both the cap centreline and middle of the cartridge.

Resealability: The disc of the cartridge will be penetrated a specified number of times with a needle, after which the calculated force will be applied onto the sample for no less than 60 seconds.

Plunger Force: Any fluid will be removed from the drug product, along with he septum, so that, at 50 mm/min, the plunger is driven along the barrel and the peak initiating force is recorded, as well as the maximum glide force.

Dimensions: The overall diameter, the plunger insertion depth and the distance from the bottom of the cylinder to the marked centre of the cap can be measured in mm using profile projectors or microscope.

The purpose of the above test is to ensure these factors do not interfere with the fit and function of the identified compatible NIS.

Scan the QR code to see our ISO 11608 / 11040 testing services

Devices & Standards

NIS - USP 1207 Closed Container Integrity (CCI) testing refers to the process of evaluating the integrity and sterility of sealed medical device containers, such as pouches, blister packs, syringes, or vials. It plays a vital role in maintaining product quality and protecting patients from potential contamination risks. By conducting rigorous CCI testing, medical device manufacturers can ensure that their products remain uncontaminated throughout their entire lifecycle. This testing verifies that the packaging maintains its integrity during storage, transportation, and usage, safeguarding the product's effectiveness and minimising the risk of harm to patients.

At MET, we offer both destructive and non-destructive CCI testing methods:

- Hydrogen Gas Detection – A non destructive, highly sensitive method of leak detection with easy method transferability and best case detection limits of 0.1-2µm defects. This is a qualitative method but may also be quantitative if requested.

- Methylene Blue Dye Ingress – A destructive, probabilistic method that is familiar to both industry and regulatory bodies and has been used for decades. Dye Ingress has best case detection limits of anywhere between 20-50µm. Usually a qualitative method, this may also be quantitative when combined with UV-Spectroscopy.

6. NIS Cannula with Luer port - ISO 80369 -6, -7 and -20

The purpose of Luer Verification testing is to verify two assemblies with male and female Luer mating features fit securely and tightly, enabling the assemblies to be fit for purpose in real life medical applications. In addition, Luer Verification testing checks the performance of the two connected assemblies cannot be easily compromised.

What is a small-bore connector?

In patient care settings, such as hospital bedsides and outpatient clinics, small-bore connectors and connections are used to combine the different medical devices, components, and accessories of a gas or liquid delivery system. The connected parts include such things as tubing, syringes, fluid bags, gas lines, filters, backflow preventers and so on. In combination, these parts make up sub-assemblies and assemblies.

***Figure 1** – Examples of cannula connectors, attached to a steel reference connector.*

What is a Luer?

A Luer is a standardised connection type based on a conical taper design. Luer fittings rely on this taper and the friction between the mating surfaces to provide quick, tight, leak-proof seals between male and female Luers.

Luer Slip - There would be no threads, the two assemblies would be just pressed together and held by friction.

Luer Lock – Has special threads, allowing a more secure connection.

***Figure 2** – An example of two small bore connectors, in this case syringes with male Luer fittings; one with a Luer lock male fitting and the other with a Luer slip male fitting.*

***Figure 3** – An example of two assemblies being connected together. One with a Luer slip connestion, the other with a Luer lock connection.*

Equipment

During Luer verification testing, there are advantages to using the assembly that will actually be connected with sample in real life application. However, MET have a supply of calibrated steel reference connectors, with male and female mating features, that can be mated with the sample. Additionally, due to the ISO 80369 standard outlining specific parameters (forces, torques, pressures) that need to be applied onto the sample, MET have instruments that can mimic unscrewing the assemblies, pulling the assemblies apart, overtightening the assemblies and connecting the assemblies together (also referred to as Ease of Assembly).

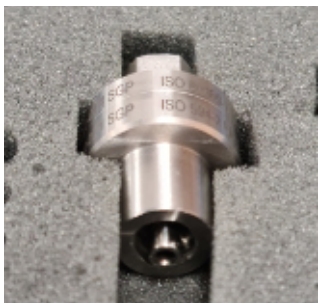


***Figure 4** – A Male Steel Reference Luer Lock Connector for testing Female Luer Connectors.*

Method	Standard and Annex	Acceptance Criteria	Reference Connector					
			Female			Male		
			C1	C2	C5 (Luer Slip)	C2 (Luer Slip)	C4	C6
Air Leakage (Leakage by Pressure Decay)	(ISO 80369-20 Annex B)	The Luer connector shall not leak by more than 0.005Pa·m³/s	+		+	+	+	
Resistance to Separation from Axial Load (Separation Force)	(ISO 80369-20 Annex F)	The fitting assembly must resist separation from axial load		+	+	+		+
Resistance to Separation from Unscrewing (Unscrewing Force)	(ISO 80369-20 Annex G)	The fitting assembly must resist separation from unscrewing	+				+	
Stress Cracking followed by Positive Pressure Liquid Leakage	(ISO 80369-20 Annex E) (ISO 80369-20 Annex C)	There must be no leakage of water sufficient to produce a falling drop of water	+		+	+	+	
Positive Pressure Liquid Leakage	(ISO 80369-20 Annex C)	There must be no leakage of water sufficient to produce a falling drop of water	+		+	+	+	
Sub Atmospheric Positive Pressure Air Leakage	(ISO 80369-20 Annex D)	The Luer connector shall not leak by more than 0.005Pa·m³/s	+		+	+	+	
Resistance to Overriding	(ISO 80369-20 Annex H)	The fitting assembly must not show evidence of overriding		+				+

***Table 1** – Test methods taken from ISO 80369-20*

Standard

These Luer Verification tests are generally qualitative, they do not produce a quantifiable result but, rather, the test is to see if the assembly of the syringe has been affected.

The methods stated in ISO 80369-20, are as follows:

- Air Leakage (Leakage by Pressure Decay)
- Resistance to Separation from Axial Load (Separation Force)
- Resistance to Separation from Unscrewing (Unscrewing Force)
- Stress Cracking followed by Positive Pressure Liquid Leakage
- Positive Pressure Liquid Leakage
- Sub Atmospheric Positive Pressure Air Leakage
- Resistance to Overriding

Plunger Movement

MET believe that it is not only important to ensure that products are protected during transit, it is also essential to ensure that they remain sterile. That is why we have developed a bespoke and customisable method for determining the movement of plungers in Prefilled Pens (PFPs) and Prefilled Syringes (PFSs) during air transport.

Scan the QR code to see our ISO 80369 testing services

References:

1. ISO 11040 Prefilled syringes
2. ISO 11608 Needle-based injection systems for medical use — Requirements and test methods
3. ISO 80369 Small-bore connectors for liquids and gases in healthcare applications (replaces ISO 594)
4. What is an ISO 80369-7 Compliant Luer? – The New Luer Standard | ISM (industrialspec.com)
5. Difference between Luer slip and Luer lock syringe — RayMed
6. Syringe, Luer Slip/Lock 3 Parts Latex-Free | Taiwantrade.com
7. Small-bore connectors for liquids and gases in healthcare applications — Part 7: Connectors for intravascular or hypodermic applications (ISO 80369-7:2021)
8. How to Give a Subcutaneous Injection Using a Pre-filled Syringe -https://www.youtube.com/watch?v=VikRTpwgyeo
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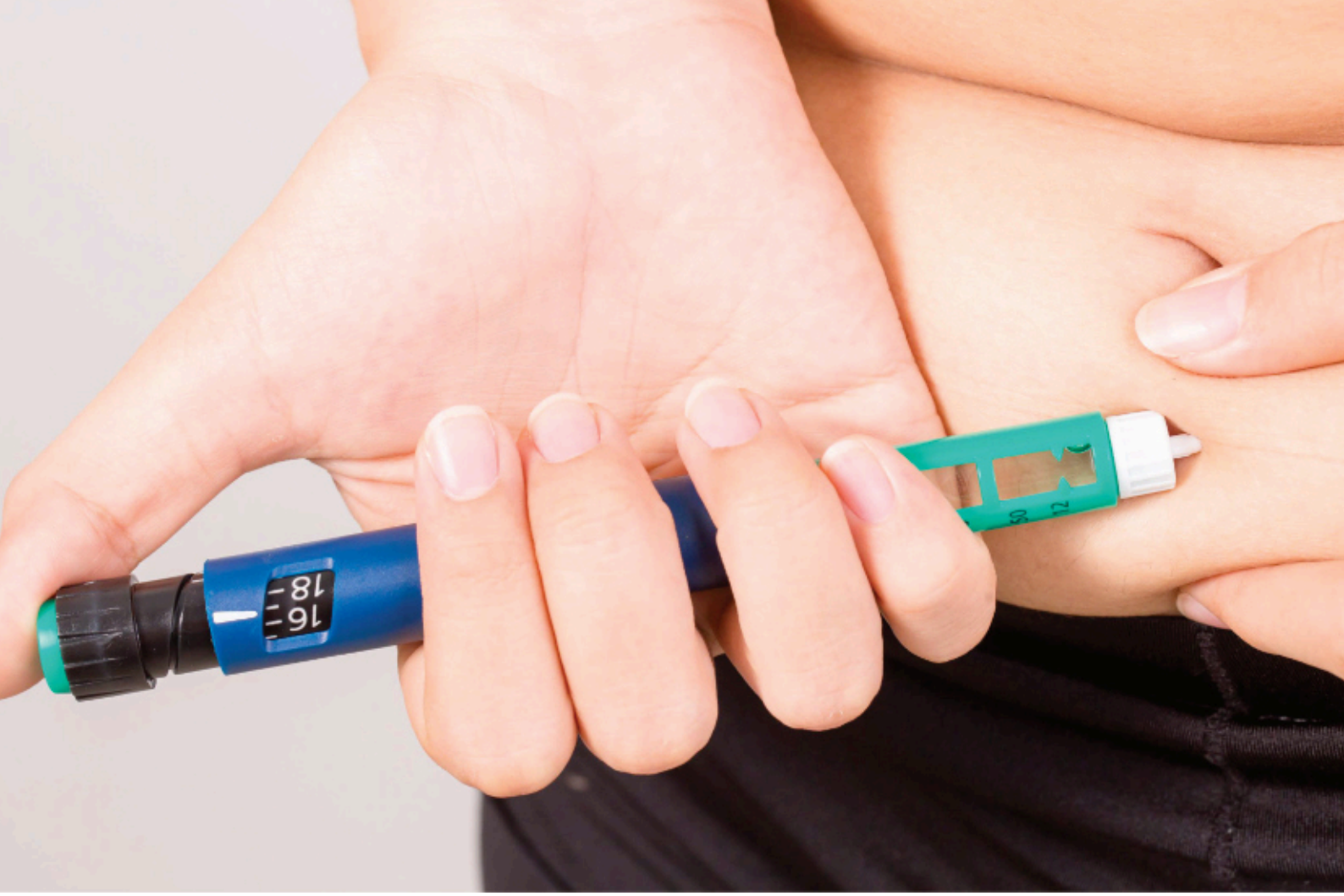
10. https://www.fortunebusinessinsights.com/industry-reports/prefilled-syringes-market-101946
11. Auto-injector- ISO 11608-5, regulatory requirements & Analytical Services https://www.westpharma.com/blog/2023/january/auto-injector-iso-11608-5-regulatory-requirements-analytical-services
12. Prefilled Syringes Market to Exhibits Remarkable Growth | $15,735.49 Million by 2030 https://bit.ly/pharmiweb-com-prefilled-syringes



Design Verification Vs Design Validation

Introduction

Design Verification and Design Validation are both crucial steps in the timeline of bringing a medical device to market; ensuring the manufactured medical device is safe, effective and achieves its intended use. Although closely linked, Design Verification and Design Validation have distinct definitions. Design Inputs and Design Outputs are integral to the Design Verification; both CFR 820.30 and ISO 13845:2015 describe the requirements for both Design Inputs and Design Outputs.

Definitions

Design Verification is the confirmation that design outputs meet design inputs ensuring the design of the device is efficient. Put simply, it confirms that the design of your device is correctly aligned with the required specifications. Generally, the Design Verification work and testing occurs during the device development stage.

Design Validation occurs once the Design Verification has been completed and documented. It is the process of gathering verifiable evidence to ensure that the established requirements align with the user needs and intended uses, thereby confirming their compliance. Design Validation shall be performed on initial production lots or batches, or their equivalents.

Design Inputs are the required physical and performance characteristics used as the basis for the device design. These need to be based on the user needs and intended use(s) of the device, which can include: Safety, Reliability, Human Factors, Device Functionality, Physical Characteristics, Labelling and information derived from similar devices (if applicable).

Design Outputs describe the individual components (assemblies and subassemblies) that combine to create the medical device. The device manufacturer will need to create and maintain the appropriate documentation for documenting the design outputs that will allow the evaluation of conformance to the design inputs.

Design Verification and the ISO 11608 Series

The ISO 11608 series of standards play a crucial role in the development of Needle Injection Systems (NISs), encompassing the process of design verification to ensure these devices align with the designated specifications (Design Inputs). ISO 11608-1:2022 provides comprehensive guidelines that outline testing methodologies to validate the accuracy and effectiveness of NISs.

At the core of this process lies design verification, which is an indispensable step to confirm that the NISs have been meticulously developed to meet their intended purposes and objectives. These purposes could span a wide range, from dosing medicinal product accurately to enhancing patient comfort during injections. The ISO 11608 series lays out the framework to ensure that these systems are not only efficient but also reliable in their performance.

ISO 11608-1:2022 covers multiple key areas of testing. It encompasses sampling plans, and pre-conditioning criteria, which prescribe the necessary steps to prepare the samples for testing. These elements collectively contribute to the establishment of a robust verification process designed to provide a high level of confidence in the functionality and safety of NISs.

However, it is crucial to recognise that the primary focus of ISO 11608-1:2022 lies in validating the design of Needle Injection Systems against their intended requirements and specifications. While this standard plays a pivotal role in ensuring the efficacy of NISs, it does not encompass the definition of batch or lot release acceptance criteria related to the broader manufacturing process.

The ISO 11608 series of standards serves as a comprehensive compass for the design verification of Needle Injection Systems. Through their meticulous guidelines, these standards promote a thorough and systematic approach to testing, enabling manufacturers to validate that their NIS designs are aligned with their intended purposes and functions.

References

1. 21 CFR 820.30
2. ISO 13485:2016
3. ISO 11608-1:2022
4. The Art of Defining Design Inputs And Design Outputs https://bit.ly/greenlight-guru-art
5. Design Control Guidance https://www.fda.gov/media/116573/download

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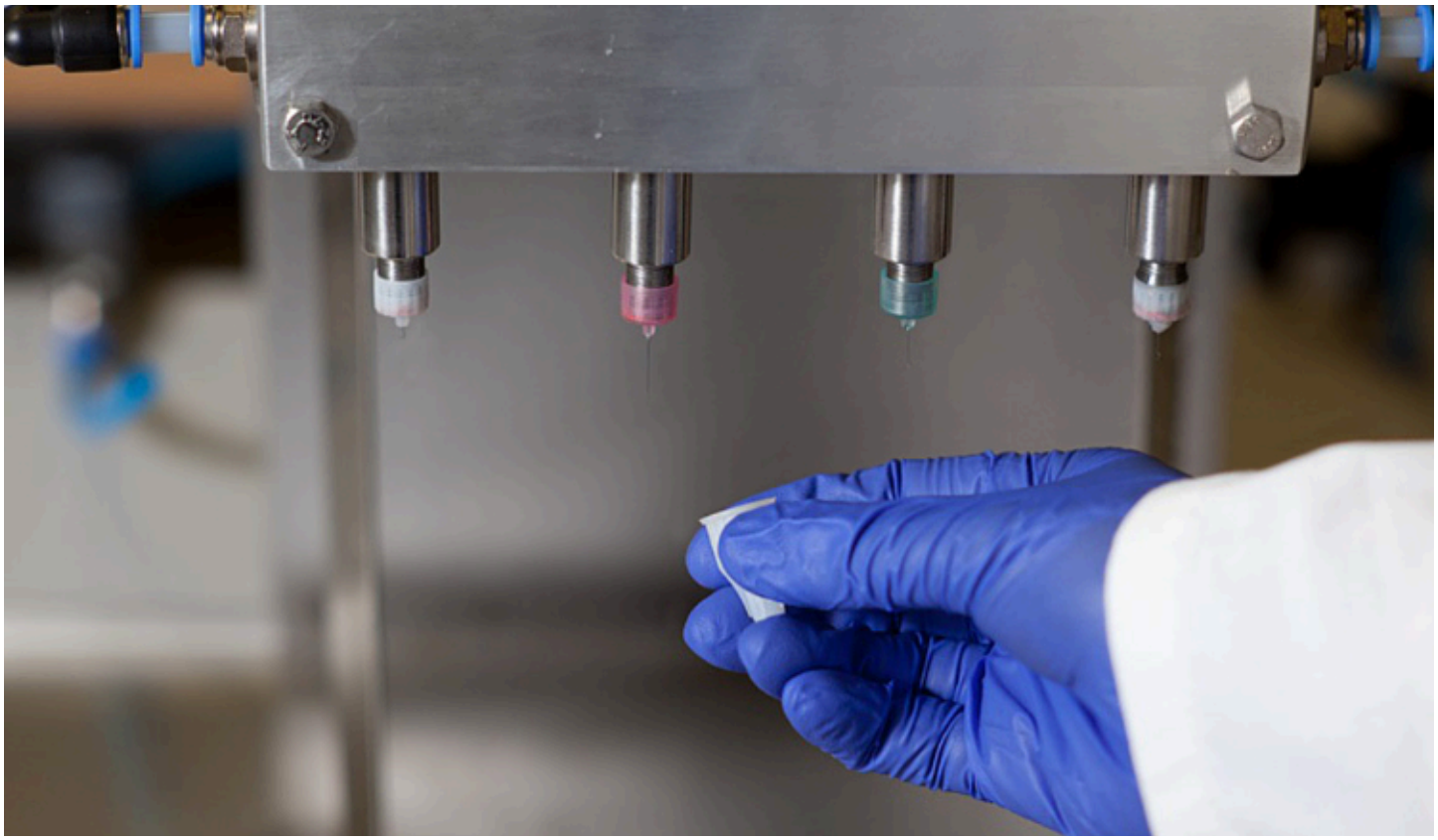


Verification of Injectables in Transport and Storage

Introduction

Stability Testing and Distribution Testing play crucial roles in ensuring the safety and effectiveness of medical devices. Stability Testing, which includes Accelerated Aging and Real-Time Aging, assesses the product's performance and characteristics over time to simulate the effects of aging. This type of testing provides valuable insights into the device's durability, reliability, and quality throughout its expected lifespan.

Distribution Testing, on the other hand, focuses on evaluating the impact of transportation and handling on the medical device. It replicates the various environmental conditions encountered during transit, such as vibration, temperature changes, and mechanical stress. This testing helps identify potential risks and vulnerabilities in packaging, ensuring the device's integrity and functionality are maintained during transport.

Stability Requirements

Stability testing is a vital aspect of medical device testing, ensuring that devices maintain their intended performance and characteristics throughout their anticipated shelf life. Two key components of stability testing are Accelerated Aging and Real-Time Aging.

Accelerated Aging: This testing method employs intensified environmental conditions, such as elevated temperatures and humidity, to expedite the aging process of the medical device. By subjecting the device to accelerated aging, potential long-term effects can be observed within a shorter timeframe. This enables manufacturers to assess the device's durability, functionality, and material properties under extreme conditions.

Real-Time Aging: Real-time aging involves exposing the medical device to normal storage conditions over an extended period. This testing approach reflects the device's performance under typical usage scenarios and assesses its long-term stability and reliability. Real-time aging provides valuable data on the device's degradation patterns, material compatibility, and overall performance over time.

For guidance on stability testing, the pharmaceutical industry's Committee For Proprietary Medicinal Products (CPMP) document titled "Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products" can serve as a valuable reference. This document provides comprehensive recommendations and methodologies for stability testing, which can be adapted to the specific requirements of medical device combination studies.

Distribution Testing

Distribution testing is an essential component of medical device testing that evaluates the effects of transportation and handling on the integrity and functionality of devices during transit. It simulates the various conditions encountered during distribution, including vibration, temperature fluctuations, and mechanical stress, to identify potential risks and ensure the device remains safe and effective upon arrival.

Common Distribution Test Standards

ASTM D4169-22 (FDA Recognition number 14-576)

ASTM D7386-16 (FDA Recognition number 5-113)

ISTA 3A-2018 (FDA Recognition number 5-126)

One widely recognized standard for distribution testing in the medical device industry is ASTM D4169, "Standard Practice for Performance Testing of Shipping Containers and Systems." This standard outlines procedures for subjecting packages and products to a series of rigorous tests to simulate real-world distribution scenarios. It provides guidelines for selecting appropriate test levels, defining test durations, and evaluating the performance of the packaging system.

By adhering to the ASTM D4169 standard, medical device manufacturers can assess the packaging's ability to withstand the challenges of transportation and ensure the device's integrity is maintained throughout the distribution process. This enables them to make informed decisions regarding packaging design, material selection, and protective measures, to mitigate potential risks.

Assurance Levels

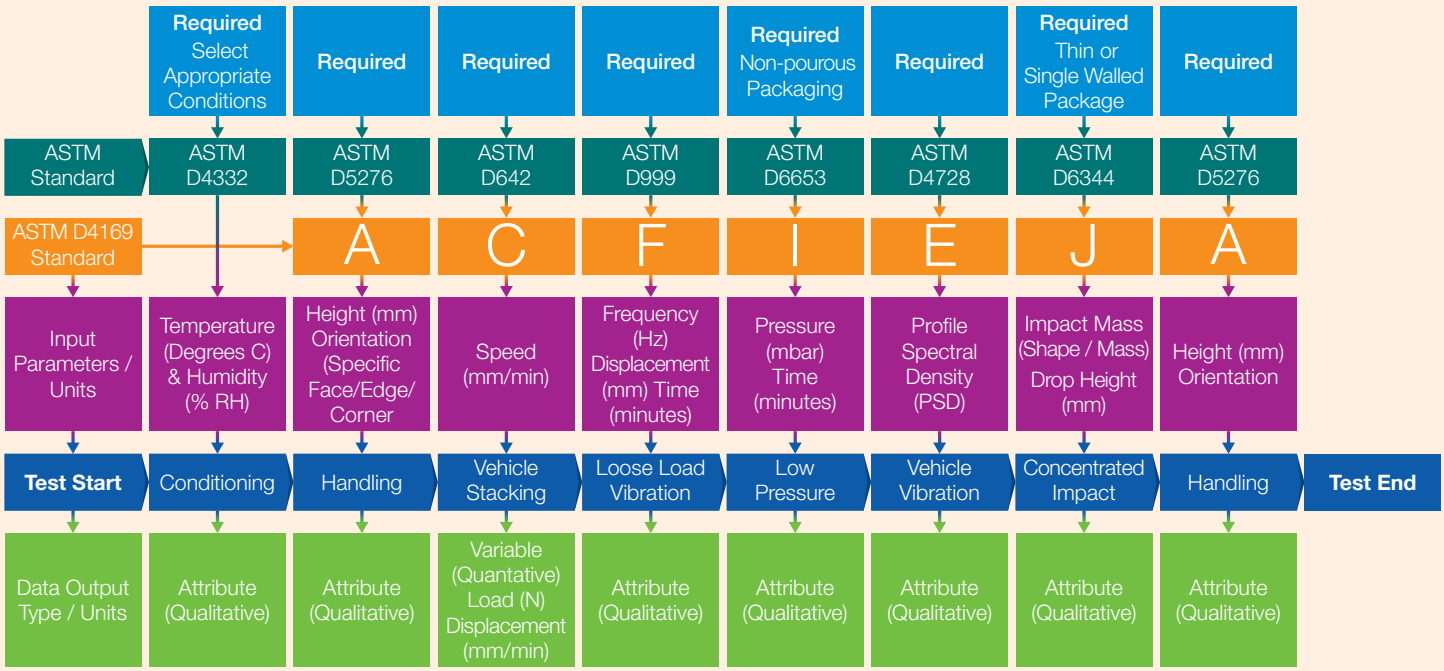
ASTM D4169-22 provides assurance levels that reflect the intensity of transit testing, aiding in determining packaging robustness. For instance, let's consider drop testing for packages under 9.1kg. At Assurance Level I, the package undergoes drops from 610 mm height. Assurance Level II involves drops from 381 mm, and Assurance Level III uses

229mm drops. These levels align with decreasing risk tolerance; higher assurance levels involve more extreme testing.

Similarly, in vehicle stacking (Schedule C), the F-Factor for shippers differs based on assurance levels. For containers like corrugated or plastic, Assurance Level I uses an F-Factor of 10.0, Level II uses 7.0, and Level III uses 5.0. Here again, higher assurance levels signify more rigorous testing due to elevated risk.

Assurance level choices are strategic. Sterile products often necessitate higher assurance, aligning with ISO 11607-1 recommendations. Assurance Level I might be chosen to ensure the package's integrity in extreme conditions, critical for sterile medical items. In contrast, non-sterile products might be tested at Level II or III, considering their lower vulnerability. These assurance levels reflect a well-calibrated risk management approach, ensuring packaging reliability under varied conditions.

ASTM D4169 (2022) Distribution Cycle 13 Overview



Attribute Results

Attribute results are qualitative or categorical data that indicate the presence or absence of a specific characteristic or attribute.

Variable Results

Variable results are quantitative data that can be measured or expressed numerically, representing a range or continuum of values.

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Distribution Testing Types

Conditioning

Conditioning in transit testing involves subjecting packaging and products to predetermined temperature and humidity levels before testing, mimicking real-world environments. ASTM D4332 sets guidelines for this process. Conditioning stabilises packaging materials and products, enabling them to reach equilibrium with the testing environment. This is particularly important for evaluating compression effects, like vehicle stacking, where packages endure sustained pressure during transit.

Conditioning prevents variables, like initial moisture content, from skewing test results. For example, during vehicle stacking, packages experience compression from other packages' weight. Conditioning ensures consistent material response, reflecting accurate stacking-related performance. This step enhances the reliability of transit testing results, making assessments of packaging performance, especially concerning compression behaviour, more precise and applicable to real-world scenarios.

Drops / Handling

Drop or handling testing is a critical aspect of distribution testing that focuses on evaluating the ability of medical devices to withstand the impact and stresses incurred during handling, loading, and unloading processes. This testing simulates accidental drops or mishandling scenarios that can occur during transit or while the device is being used in real-world settings.

During drop or handling testing, the device is subjected to controlled drops from specified heights onto different surfaces, such as rigid or semi-rigid materials, to assess its structural integrity and functionality. This helps identify potential weaknesses in the device's design, materials, or packaging, enabling manufacturers to make necessary improvements to enhance its robustness and protect it from damage during transportation and handling.

Compressive Load

This test assesses the device's ability to withstand compressive forces that can occur during transportation and storage. ASTM D642 provides guidelines for conducting compressive load testing by subjecting the device to controlled and gradually increasing forces until the desired load is achieved.

This testing helps identify potential weaknesses in the device's structural integrity and packaging, ensuring it can withstand the pressures encountered in real-world scenarios and maintain its functionality and safety during transit.

Random Vibration

Random vibration testing is a method used in distribution testing to simulate the unpredictable and multi-directional vibrations experienced during transportation.

This type of testing subjects the medical device to vibrations with varying frequencies and amplitudes, replicating real-world conditions. Random vibration testing is effective in identifying weaknesses in the device's design and packaging, as it covers a broad range of vibrations and assesses its ability to withstand random and irregular motion.

Sine Vibration

Sine vibration testing, on the other hand, focuses on subjecting the medical device to vibrations at a single frequency and amplitude. Unlike random vibration testing, sine vibration testing allows for precise control of the vibration parameters.

This type of testing is particularly useful for evaluating the device's response to specific frequencies that may be encountered during transportation or in certain usage scenarios. Sine vibration testing helps assess resonance effects and potential vulnerabilities in the device's construction that may arise under specific vibration conditions.

Impact

Concentrated impact testing is an important component of the overall testing regime for medical devices. This type of testing focuses on evaluating the device's ability to withstand localised impact forces, such as those caused by drops or accidental impacts during handling. During concentrated impact testing, a specific point or area of the device is subjected to a controlled and concentrated impact force.

This testing helps identify vulnerabilities, potential structural failures, or functional issues that may occur due to impact events. By conducting concentrated impact testing, manufacturers can ensure that their medical devices are robust enough to withstand accidental impacts and maintain their integrity and functionality in real-world scenarios.

Low-Pressure / High-Altitude

Low pressure testing is a critical component of medical device testing, specifically for devices intended for use at high altitudes or in environments with reduced atmospheric pressure. This type of testing assesses the device's performance and integrity under low-pressure conditions, simulating scenarios such as air travel or high-altitude deployments.

By subjecting the device to controlled low-pressure environments, manufacturers can evaluate its functionality, structural integrity, and potential risks associated with pressure differentials. Low pressure testing helps ensure that medical devices can withstand and operate effectively in environments where atmospheric pressure is significantly reduced, providing valuable insights into their reliability and safety.

Conclusion

Stability and distribution testing play indispensable roles in the design verification testing of combination devices, underscoring their crucial importance in ensuring the safety, efficacy, and reliability of these complex medical products. Through stability testing, accelerated aging and real-time aging provide valuable insights into the device's durability, reliability, and material properties over time. Distribution Testing, including handling, vibration, and compressive load tests, simulates real-world transport conditions, identifying potential risks and vulnerabilities in packaging and ensuring device integrity.

Together, these testing methodologies contribute to comprehensive risk assessment, aiding in regulatory compliance and facilitating informed decision-making throughout the device development process. Incorporating stability and distribution testing as integral components of design verification is imperative for ensuring the successful and safe deployment of combination devices in clinical practice.

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Combination Device Project Examples

MD, MV, DVT, Stability & Biocompatibility Testing of a 1mL PFS (Type D1 NIS)

In order to submit a new 1mL PFS to the FDA, a client approached MET to carry out a full validation of the device, which proceeded as follows:

1. Method Development (MD) was carried out in order to ensure the PFS test rigs were able to withstand the forces required within the tests (Cap Removal Force, Break Loose & Glide Force) and that the samples fit well, as well as to create tests on the Test Stands (30 Samples)
2. Method Validation (MV) was performed on the tests within the DVT project (below) to ensure that the repeatability and reproducibility were acceptable, with three technicians carrying out each test on three occasions with 10 samples (90 Samples)
3. Design Verification Testing (DVT) was conducted using the developed and validated methods, at cool, standard and warm conditions (according to ISO 11608):

DVT Test Sequence	Sample Quantity
Pre-Test Visual Inspection	120 (All)
Cap Removal Force	60
Break Loose & Glide Force	
Dose Accuracy	
Post-Test Visual Inspection	120 (All)
TOTAL Sample Quantity	**120**

4. A stability project was completed to ensure design verification throughout the product's shelf life of 4 years, with both real time and accelerated ageing as follows:

Ageing	Time Point	Sample Quantity
Real Time Ageing (5 ± 3°C)	Time Zero (Control)	60
	3 Months	60
	6 Months	60
	12 Months	60
	24 Months	60
	36 Months	60
	48 Months	60
Accelerated Ageing (25 ± 2°C / 60 ± 5% RH)	RTE 12 Months	60
	RTE 24 Months	60
	RTE 36 Months	60
	RTE 48 Months	60
TOTAL Sample Quantity		**660**

**RTE = Real Time Equivalent*

5. Biocompatibility testing was carried out according to ISO 10993, as follows:
   1. Biological Evaluation Plan (BEP)
   2. Chemical Characterisation
   3. Toxicological Risk Analysis (TRA)
   4. Cytotoxicity
   5. Pyrogenicity
   6. Irritation
   7. Sensitisation
   8. Biological Evaluation Report (BER)

Method Validation and Stability Testing of a 1mL PFS-SD (Type D1 NIS)

1. Method Validation was performed to ensure that the repeatability and reproducibility were acceptable, with three technicians carrying out each of the tests on three occasions (90 Samples)
2. Stability Testing was completed according to the following test sequence:

Test Sequence	Sample Quantity
Break Loose & Glide Force	30
Safety Feature Activation Force	
Dose Accuracy	36
TOTAL Sample Quantity	**66**

At the following timepoints:

Ageing	Time Point	Sample Quantity
Real Time Ageing (5 ± 3°C)	Time Zero (Control)	66
	1 Month	66
	3 Months	66
	6 Months	66
Accelerated Ageing (25 ± 2°C / 60 ± 5% RH)	RTE 1 Month	66
	RTE 6 Months	66
	RTE 12 Months	66
TOTAL Sample Quantity		**462**

**RTE = Real Time Equivalent*

Batch Release Testing of an AutoInjector (Type D1 NIS)

Batch release testing, i.e. the client sends 20 samples each time a new batch is produced, was carried out over several years according to the following test sequence:

Test Sequence	Sample Quantity
Visual Inspection	20 (All)
Cap Removal Force	10
Needle Extension Length	
Activation Force	10
Delivered Dose	
Delivery Time	
TOTAL Sample Quantity	**20**

Method Validation and ISO 11608 Study of Multi-Dose Pen (Type C NIS)

1. Method Validation was performed to ensure that the repeatability and reproducibility were acceptable, with three technicians carrying out each of the tests on three occasions (540 Samples Total, 60 per technician per occasion)
2. Testing was carried out according to the following test sequence, to investigate ISO 11608 Dose Accuracy, as well as some force test requirements:

Test Sequence	ISO 11608 Conditioning	Sample Quantity
Dose Accuracy	Dry Heat	60
	Cold Storage	60
	Free Fall	60
	Cool	60
	Standard	60
	Warm	60
	Vibration	20
Last Dose Accuracy	4+ Hours at 23 ± 5°C / 50 ± 25% RH	60
Cap Detachment Force	4+ Hours at 23 ± 5°C / 50 ± 25% RH	30
Cap Attachment Force	4+ Hours at 23 ± 5°C / 50 ± 25% RH	
Cartridge Holder Removal (Axial Load)	4+ Hours at 23 ± 5°C / 50 ± 25% RH	
Cartridge Holder Removal (Side Load)	4+ Hours at 23 ± 5°C / 50 ± 25% RH	30
Injection Force	4+ Hours at 23 ± 5°C / 50 ± 25% RH	30
TOTAL Sample Quantity		**500**

3. Cartridge testing was completed as per the following sequence, according to ISO 11608-3:

Test Sequence	Sample Quantity
Meniscus	10
Resealability	20
Coring	10
TOTAL Sample Quantity	**40**

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Cormica Ltd
12-18 Grosvenor Gardens,
5th Floor, London,
UK, SW1W 0DH

www.cormica.com
t +44 (0)1329 226600
e info@Cormica.com

Medical Engineering Technologies Ltd
Unit 16, Holmestone Road,
Dover, Kent,
CT17 0UF, UK

www.met.uk.com
t +44 (0)1304 213223
e sales@met.uk.com

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