

DESIGN VALIDATION TESTING – DRUG DELIVERY DEVICES

From a regulatory perspective, Mark Turner, Managing Director, Medical Engineering Technologies, provides a summary of the current requirements of parenteral device manufacturers in the area of design validation testing.

Design validation testing (DVT) is an important component of the Product Master File for all medical devices, including those used for delivering drugs and/or biologics to their target in the body.

Although this article uses prefilled syringes as an example, the principles apply to just about any drug presentation that is not a capsule, tablet or pessary (unless it has an applicator). It is a review of the testing required to demonstrate product performance.

As might be expected, the place to start with design validation is a risk analysis. This is likely to identify drug efficacy and product safety as the key areas to examine, in short: dose accuracy, toxicity, risk of infection and mechanical risk. Assuming that the manufacturing process delivers the correct materials in the correct place and in the correct quantities, the factors influencing dose accuracy will be the syringe design and its stability, toxicity will be largely governed by material selection and stability, infection control will be a matter of providing robust sterilisation processes and sterile barrier packaging and, finally, other safety factors to consider include needlestick injury and the possibility of damaged components.

STANDARDS

The relevant industry standards are:

- ASTM D 4169 Standard Practice for Performance Testing of Shipping Containers and Systems
- ISO 10993 Biological evaluation of medical devices
- ISO 11040 Prefilled syringes
- ISO 11608 Needle-based injection systems for medical use -- Requirements and test methods
- ISO 80369 Small-bore connectors for liquids and gases in healthcare applications (replaces ISO 594)
- ISO 11607 Packaging for terminally sterilized medical devices

“Due to a high incidence of incorrect connections being made in practice, ISO 594 has been replaced by ISO 80369 which describes specific connector dimensions for different applications.”

- ASTM F 1980 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.

DOSE ACCURACY

There are many aspects to ensuring dose accuracy. Some of these come from production processes, for example injectable viscosity, fill-volume and active pharmaceutical ingredient (API) concentration. Others come from the delivery system, including syringe dimensions, effectiveness of actuation and maintenance of formulation (chemical and volume) in storage and transit. The transfer of the drug into the patient must also be effective and without leakage.

Dose accuracy is generally measured gravimetrically. Whilst the balance will be very accurate, attention must be paid to the differences between injecting in air and in flesh. *In vitro* extrusion of the syringe contents will be subject to evaporation, spraying and the retention of a bead of fluid at the needle tip. All of which could produce inaccuracy relative to an *in vivo* administered dose.

ISO 11608 and the US FDA Guidance, *Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4*, provides a number of tests to be considered. **Break-loose force:** the force required initially to move the syringe plunger. This can



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influence the dose accuracy and the speed of injection. Difficulty in operating the syringe due to high break-loose force could cause misplacement, whilst an unrestrained plunger could move in transport.

Glide force: the force required to keep the syringe plunger moving. This can influence the dose accuracy in a similar way to the break-loose force.

Separation force: the force required to remove the needle from the syringe. The FDA recommends the use of a bonded needle to prevent its separation. If the needle is not bonded, the connectivity to any downstream system is important and its integrity and reliability should be demonstrated. Note that due to a high incidence of incorrect connections being made in practice, ISO 594 has been replaced by ISO 80369 which describes specific connector dimensions for different applications.

Unscrewing torque: ISO 11608 gives values for the force required to remove needles which are screwed onto the syringe.

Ease of assembly: another ISO 11608 requirement relating to re-usable pen injectors.

Resistance to overriding: a requirement of screw-on needles and Luer connectors, over-tightening of the needle could damage the thread and reduce the security of the connection.

Stress cracking: this primarily relates to the stress placed upon the male Luer of the syringe by the needle, but other forms of stress cracking should be considered from things such as a mechanical or chemical stress, all of which can lead to leakage or particle generation.

Validation of graduation markings: this is a requirement for markings on a syringe barrel or within a dispensing system (e.g. a pen injector). Often the full contents of a syringe will be dispensed and markings are not required. Variable dose dispensers do have markings which can be in the form of a dose selection dial (don't forget to measure the forces required to operate the dial), or on the syringe barrel if there can be a clinical need for a partial injection.

Dead space: air bubbles in the syringes could expand in air transport (causing leakage) or allow oxidation of active ingredients.

Coring needle test: needle blockage will interfere with correct dosage.

Seal integrity testing: this is required to demonstrate that there is no loss of dosage or ingress of liquids and should include verification of any connections, such as Luers or screw-on needles. This can be a difficult test to perform, especially when the syringe is hidden inside an auto-injector. Trace gas leak detection can be applied to good effect as can, in some cases, dye ingress. ISO 80369 gives visual inspection methods using a pressurised system, which should be included in a design validation programme but are not of adequate sensitivity to be used unsupported.

ISO 11608 gives a lot of information about dose accuracy, particularly for products which can be used more than once, such as insulin or growth hormone pens. There is a requirement to maintain the dose accuracy at all cartridge positions, at all dose levels and for the final dose from a cartridge.

Actuation forces are also important for auto-injectors, for example in cases where the force must be such that the device can be operated easily in an emergency situation. In addition, because of the automatic nature of these devices the user cannot verify the insertion of the needle. Therefore, the needle insertion depth and duration of dosing need to be tightly controlled to ensure that the dose is delivered correctly.

BIOCOMPATIBILITY & TOXICITY

An initial review of biocompatibility might suggest that ISO 10993 provides all the answers, but it does not. ISO 10993 considers how a device contacts a patient and for how long. For a prefilled syringe the pathway is generally clear, blood path indirect, short term contact. However, the modes of testing given in the standard do not consider that the contents of the syringe may have been stored in their container for two years or more, or that some devices are used repeatedly for chronic conditions.

The testing chart given in ISO 10993 (with the additions from the associated FDA Guidance) indicates that the required tests for short term contact are: cytotoxicity, irritation, sensitisation, acute toxicity, pyrogenicity and haemocompatibility. In addition, extensive extractables and leachables analysis should be included to account for the risk of the transfer of material into the injected fluid

during storage. This need is likely to be highlighted in future versions of ISO 10993, as the emphasis moves from animal testing to chemical analysis. The extractables and leachables study should include consideration of the production processes and materials, the packaging materials and labelling, and, of course, the syringe components and their possible sources of contamination. Particle generation should also be considered in addition to chemical contamination.

For treatments addressing chronic conditions it may be necessary to address genotoxic and chronic toxicity endpoints. In these cases, extremely low levels of migrating material are tolerated. In all cases a toxicological risk analysis should be considered.

STERILITY & STABILITY IN STORAGE & TRANSIT

Parenteral products might be rendered sterile by terminal sterilisation (ethylene oxide, radiation or autoclave) or they may be assembled in an aseptic environment. It is not sufficient to demonstrate that the injectable is sterile at the end of this process: it must remain sterile right through to the point of delivery.

Guidance on the maintenance of sterility comes from ISO 11607. Once sterilisation and packaging processes are validated, the shelf-life and transit security can be addressed. The ageing process can be accelerated by the application of methods set out in ASTM 1980 or the ICH Guidelines. Apart from syringe integrity tests, seal strength and integrity tests should be applied to any sterile outer barrier (e.g. blister or pouch).

ASTM D 4169 provides a framework to simulate vibration and handling in transit, whilst the US Federal Aviation Authority tells us what pressure to expect during air transit. We recommend confirmation of sterile barrier performance following transit and an assessment of pressure changes on the volume of the syringe contents. Also particle generation during this phase of the product lifecycle might be considered (due to vibration in transit).

Similarly the sterility of the product should be confirmed at the end of the product storage life. This testing can be combined with an examination of performance aspects such as delivery forces and volumes, which may have been influenced by changes in the fluid, the siliconisation of the syringe or the composition of the stopper.

MECHANICAL SAFETY

Transit testing will have shown that a product remains intact up to the point of use (glass syringe not broken, needle protection in place, etc.). However, it remains necessary to examine any safety mechanism. If the needle is protected by a simple cover, its removal and re-attachment forces should be ascertained. This and any anti-needlestick mechanism should be safe and effective as recommended in the FDA's guidance document, *Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features*: which cites "connectivity to other devices necessary for use (e.g., needles, adapters, transfer systems, extension tubing, Luer connectors, and sharps prevention features)".

A final consideration is piston seal blowback (the ability of a syringe with a tip cap to hold a certain pressure on the piston).

METHOD VALIDATION

All test results reported in a DVT study should be obtained using validated methods and calibrated equipment. Often the method validation is achieved using trained technicians in a multi-operator study. If risk analysis identifies that a particular product may influence a mode of testing, or behave unusually in any particular test, these tests should be validated for that product.

CONCLUSION

Validation of drug delivery systems requires the review of a wide range of risks, standards and guides. On the one hand, not all the aspects described here are necessarily applicable to every product, and readers can probably think of many more that are. On the other, this confirms that a thorough risk analysis is required and that time must be made available for method and protocol development, followed by comprehensive testing using well characterised systems.

ABOUT THE COMPANY

Medical Engineering Technologies (MET) has successfully delivered design validation testing to medical device and pharmaceutical companies in 20 countries across Africa, Asia, Australasia, Europe and the Americas. MET knowledgeably, reliably and effectively delivers medical device and packaging testing. Services include protocol development, laboratory testing and data analysis. The laboratory is equipped for performance testing, chemical analyses and sterile barrier verification, and with accreditation to ISO 17025, customers can have complete confidence in the quality and accuracy of the results.

ABOUT THE AUTHOR

Mark Turner is Managing Director of Medical Engineering Technologies, which provides a wide range of services to engineers and project managers in the medical device industry. Turner founded MET in 1997 after 12 years of project management and device design with Smiths Medical. He has also worked as a perfusionist in the cardiac unit of Kings College Hospital (London, UK) providing experience of the application of medical devices first hand. He received a BSc in Chemistry (with Biochemistry) from the University of Wales in 1983 and has also studied astronomy, business administration, cosmology and opto-electronics.



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