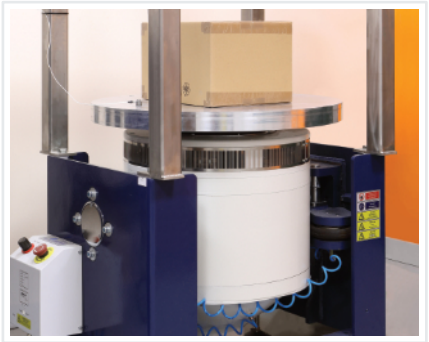
Air bubble movement measurement in simulated air transport.

Verification of Injectables in Transport and Storage

From the 26th of May 2021 many combination devices will be included in the European Medical Device Regulation (2017/745)1. Specifically this inclusion is by Article 117 of the regulation. If your delivery device is a single integral product which includes the drug and it cannot be re-used it must comply with the medical device General and Safety Performance Requirements (GSPRs)2. These requirements include verification of the devices robustness in storage and transport.

Stability Requirements

Pharmaceutical companies are familiar with the use of ICH Guidelines3 when demonstrating the stability of their formulations. These storage conditions can be used for preparing combination devices for performance testing at various points throughout their safe storage period. Indeed they are often used. For example a dose accuracy study for a biosimilar injection will use product that has been stored at the normal 4°C to 8°C because the product or other components of the formulation could denature or degrade at 25°C and alter the measured dose dispensed. From the medical device point of view the syringe is the sterile barrier packaging (GSPR 11.4).



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MEDICAL ENGINEERING TECHNOLOGIES

This, for the syringe needle cover and stopper joints would require a Closed Container Integrity Test (CCIT)4. If the combination device has secondary sterile barrier packaging there will often be a blister or a pouch pack. Both the syringe seals and any secondary packaging will be subject to ISO 11607 Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems5, as part of the GSPRs. This standard allows the use of accelerated ageing6 to obtain packaging stability information in advance of waiting for natural ageing to produce test material which has completed its recommended storage period. This is acceptable for both the secondary packaging and the CCIT. A temperature of 25°C is acceptable for this accelerated ageing. Typically, the rapid ageing for a medical device is carried out at 55°C (a condition that is not found in the ICH Guidelines). At this temperature, for a product that is normally stored at 4-8°C, an equivalent shelf life of three years would be attained in approximately 6 weeks (ASTM F1980)6. This allows the stability of the packaging to be validated well in advance of the validation of formulation related performance aspects.

Transport Requirements

Also required by ISO 11607 is confirmation of the combination devices robustness in transportation. The specific standard used for this is usually ASTM D41697. This standard gives conditioning (inputs) recommendations to simulate transit. These include stacking, concentrated impact, vibration and manual handling. There are a variety of pre-conditioning atmospheres to be applied usually for 72 hours before subjecting a shipping carton to the transit inputs. These would not be relevant for a cold chain product. For a device that is shipped without temperature control, consideration must be made of environments into which a carton may be shipped. With regard to the formulation artic

Closed container integrity testing using a trace gas technique.

or desert are likely to be the most severe. When thinking about the carton tropical (38°C/ 75% relative humidity) is usually the most severe environment. Other situations should also be considered, the most common one for delivery devices being air transport. For example, it is possible that an air bubble inside a Prefilled Syringe (PFS) would expand and contract as an aircraft changes altitude. This can cause movement of the fluid which in turn might cause a change in dose available or lead to evaporation and the deposit of residue which could block the needle aperture. These effects can be simulated in an air transit test chamber.

Conclusion

Drug device combination products are just that, multi-component systems which straddle the medicinal and medical device regulatory systems. When it comes to stability testing both pathways must be followed to demonstrate the stability of the formulation and of the packaging components. For the resistance to damage in transit, the two pathways largely overlap with consideration included of any product specific hazards that have been identified in a risk analysis.

References

1. European Medical Device Regulation (2017/745)1. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
2. MDR, Annex 1, GSPRs https://www.medical-device-regulation.eu/2019/07/23/annex-i-general-safety-and-performance-requirements/
3. ICH Q1A (R2) Stability testing of new drug substances and drug products https://www.ema.europa.eu/en/ich-q1a-r2-stability-testing-new-drug-substances-drug-products
4. Closed container integrity testing https://met.uk.com/medical-device-testing-services/packaging/ccit
5. ISO 11607 Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems https://www.iso.org/standard/70799.html
6. Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices https://www.astm.org/Standards/F1980.htm
7. ASTM D4169 - 16 Standard Practice for Performance Testing of Shipping Containers and Systems https://www.astm.org/Standards/D4169.htm