WHICH IS THE BETTER TOXICITY TESTING STRATEGY FOR COMBINATION DEVICES?

In this article, Mark Turner, President of Medical Engineering Technologies, explores the issue of toxicity testing for combination devices and asks which is the better testing strategy – ISO 10993 or extractables and leachables?

You have a prefilled drug delivery system and you are wondering how to demonstrate its biological safety. Your product is the pharmaceutical but you are now delivering it in a ready-to-use syringe or transdermal patch, an inhaler or maybe an implant.

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A pharmaceutical manufacturer needs to demonstrate that a packaging system is suitable for its intended use and that is does not introduce extraneous materials (of toxicological concern) into the formulation or degrade the formulation's performance. The formulation must also be free from process equipment related leachables at levels of toxicological concern. A medical device manufacturer needs to demonstrate that their device does not cause toxicity in its mode of use.

The US FDA definition serves both camps well: "Drug product containers and closures shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug beyond the official or established requirements."[1]

Significant progress towards the satisfaction of all these requirements can be made in a single extractables and leachables programme. A range of solvents and extraction conditions for the purposes of targeting a variety of potential leachables can be applied for both the device and the formulation packaging.

ON-BODY DEVICES

Taking an on-body insulin pump as an example, there will be the external components of the cartridge and pump that are in contact with the body. The contact is with skin in this case, whilst only internal components will contact the formulation. A leachables study can be conducted on the fluid path to obtain information on what is likely to leach into the formulation. This same information can form the "simulated use" chemical characterisation of leachates required by ISO 10993.[2]

The pharmaceutical approach still needs the extractables study to examine potential contaminants that could migrate into the formulation over a longer period. Similarly, the medical device approach will be missing information on cytotoxicity[3] and local irritation.[4] Some extra work is required in each case. Additionally, according to ISO 10993, the biocompatibility of the outside (skin contact) surface should be considered. Therefore, an extractables study should include the entire device – not just the fluid path.

EXTRACT MEDIA

A choice of media – such as 50% water / 50% ethanol – will give good information for the pharmaceutical extractable analysis and the device mid-polar leachables. The medical device extraction requires polar

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and mid-polar extracts to simulate the lipid and aqueous environments within the body (a third more polar extract must be included for invasive devices). Both study sets could use either saline or water as the polar extract medium.

When considering leachables from a pharmaceutical container, the nature of the formulation should be taken into account – is it aqueous and, if so, what is the pH; does it contain compounds that will influence migration of substances; is it non polar? To overcome this, in part of the study the leachables will need to be examined using the actual formulation. This is compatible with ISO 10993, which contains suggestions of which solvents to use but does not dictate them.

Post-extraction concentration and digestion for inorganic testing is also acceptable for both routes. For a pharmaceutical container, there may be more concern about the leachables concentration varying over time and the need for testing multiple batches. This would also be prudent for medical devices but it is not usually applied. Other additional questions for pharmaceuticals relate to bioavailability at the end of the shelf life.

ANALYTICAL METHODS

The analytical methods are also largely the same. For the extracted materials, inductively coupled plasma mass spectrometry (ICP-MS), gas chromatography–mass spectrometry (GC-MS) and liquid chromatography–mass spectrometry (LC MS) are most commonly applied. These methods allow quantification of the majority of the organic materials (across a wide range of volatilities) that might be found and any associated inorganic elements. There can be many variances for other analyses such as infrared absorbance and surface chemistry/morphology on devices and USP monograph and physicochemical analysis for pharmaceuticals.

TOXICITY ASSESSMENT

In both the pharmaceutical case and the medical device case, the chemical information gained goes on to be analysed by a toxicologist. In the toxicity risk assessment (following the analytical study), the same principles apply to both routes. Items such as the application of analytical evaluation thresholds (AET) and safety concern thresholds (SCTs) are common.[5] The Product Quality Research Institute (PQRI, Washington, DC, US)[6] has recommended that the high-risk SCT is set at 0.15 µg/day, whilst the low-risk SCT is set at 1.5 µg/day, both having been justified from toxicological and safety perspectives. Under certain conditions, such as short-term exposure or in the treatment of a life-threatening condition, the SCT can be raised above 1.5 µg/day.[7]

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IMPLANT DEVICES

What if my drug-releasing product is an implant? ISO 10993 includes a biocompatibility matrix[8] which describes the information it is necessary to obtain in order to demonstrate compliance. The matrix cross references body contact with "toxicological end points". These end points are the modes of toxicity that must be considered within a biological risk assessment. For an implant, just about everything is included: implantation, geneotoxicity, mutagenicity and chronic toxicity, to name just a few. Again, this is similar to the requirements for a pharmaceutical agent.

The requirements for an implant are more demanding than those for the surface-contacting insulin pump. Also, the "simulated use" extraction needs to be more aggressive because of the long-term contact at 37°C. There are many parts to ISO 10993. ISO 10993-18,[9] the chemical characterisation part, tells us to use exhaustive or exaggerated extraction for implants. ISO 10993-12,[10] the sample preparation part, is due for an update. It currently defines exaggerated extraction as 24 hours in the solvent at 70°C (however, this process might dissipate volatile contaminants and therefore should be accompanied by lower temperature extractions). The most aggressive possible solvent should be used, as long as it does not degrade the device in a non-representative way.

In situ degradation should also be considered for implanted devices. ISO 10993 has three sections detailing this requirement. One each for metal,[11] ceramic[12] and polymeric[13] devices.

PHARMACOPEIA TESTING

There are a variety of areas in which the USP makes requirements of pharmaceutical manufacturers. Namely, USP chapter <1663>, Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems, which is the basis for the chemical safety assessment section of USP <661.2>. This will soon be supported by two documents which are currently in draft form, USP <665> the extractables profile, and the chemical safety qualification draft USP <1665>. The latter applies to manufacturing systems, where a greater range of extraction solvents should be considered.

STUDY DESIGN

There are well-defined components and structures to be used in analytical and toxicity study design and reporting. The first step is an assessment of the input materials and processes, which is used to define what chemicals might be available from containers, devices and production methods. In pharmaceuticals, this is framed as a justification of methods used. In the device world, it is called a biological risk assessment. This is the information that goes into the study design. It contributes to identifying:

- The extraction media to be used
- The extraction conditions
- The analytical methods to be applied as well as:
  - method development
  - method quantification standards to be included
  - method validation
  - defining the sensitivity needed.

Again, the principles of study design and reporting are largely common between medical devices and pharmaceuticals.

CONCLUSION

The quick answer to the question of whether to follow extractables and leachables testing

or ISO 10993 for a combination device is that both are required. You need to prove the safety of the pharmaceutical agent and the medical device. The practical solution is that a well-designed extractables and leachables study will cover most of the requirements for medical device biocompatibility. In the pharmaceutical case, it is necessary to show that the formulation is still active to the extent expected without the addition of extraneous materials. For the medical device, we don't want to put extraneous materials into the body – whether they come from the formulation or parts of the device not in contact with the formulation.

Some additional work will be required to cover both sets of requirements but there is also a lot of overlap. Both systems have hierarchy of risk related to intimacy of body contact, although low-risk surface or transient contact devices could still be delivering into high-risk environments such as ophthalmics or intravascular.

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 North America. 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 results.

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