Does standardisation improve animal testing of medical devices?

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Abstract
Compliance with European regulatory standards in animal research could be viewed as a way of dotting the i's and crossing the t's, rather than actually holding the research to scientific scrutiny. Standardisation is important and needs improvement for *in vivo* testing of medical devices, so that it can be more than basic guidelines. Innovative research must go beyond the requirements set out in regulatory standards to enable research practices to be improved and updated.

Introduction to animal testing of medical devices
Thorough scientific testing of a medical device, such as an orthopaedic implant, requires several approaches (Figure 1), including biological testing. Testing of a novel device material involves *in vitro* assays in cell cultures and *in vivo* tests using animal models. The purpose of *in vitro* tests is usually to assess cell toxicity and DNA damage in animal and human cell lines and in primary human cells. Animals studies must be undertaken when cell studies are inapplicable – for example to study the systemic toxicological response, elimination pathway of a material, local and systemic immunological responses, or carcinogenicity of a material. Animal models can also be used to study *in vivo* chemical interactions or degradation of a material. The device materials may be injected or implanted in laboratory animals to study animal behaviour and physiology over short or long time frames. Extensive biochemical analysis can be carried out by harvesting various organs and tissues from the experimental animals.[1]

Standards for animal testing
What are the standardising bodies?
In Europe, the major standards bodies include the International Standards Organisation (ISO) and the European Committee for Standardisation, which co-operatively provide quality management systems and standard operating procedures for various types of scientific testing of medical devices. The standards are updated as new requirements and more effective procedures are established. These facilitate compliance with EU Directives 90/385/EEC,[2] 93/42/EEC,[3] and 98/79/EEC,[4] which concern active implantable devices, other medical devices, and *in vitro* diagnostic devices respectively. Fulfilment of the appropriate directive(s) and any supplements/revisions is the basic requirement to allow European conformity (CE) marking of a medical device, which enables its sale in Europe.

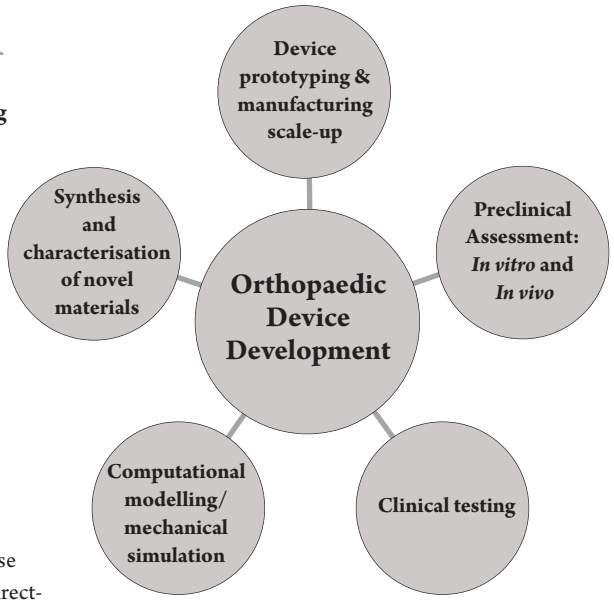
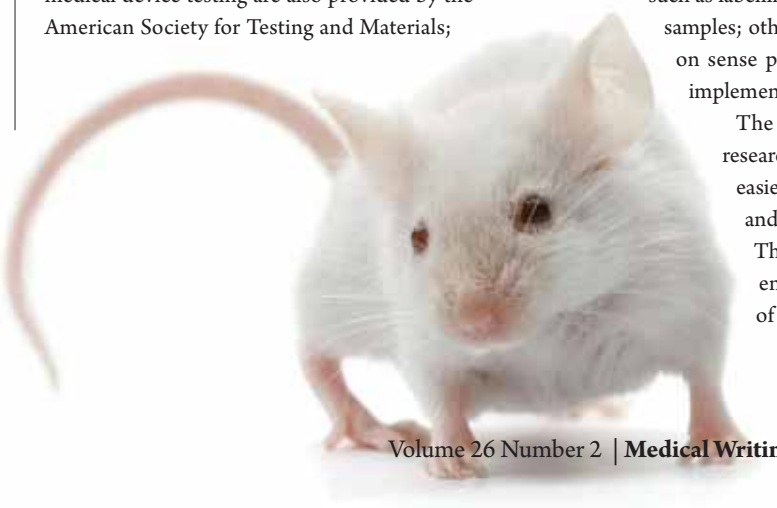


Figure 1. Orthopaedic device testing – key research processes involved in development and testing of a novel orthopaedic device

What are the main ISO standards for animal testing of medical devices?
The main ISO standard which covers quality management of animal testing, in addition to the quality management of all stages of medical device development, is ISO13485;[5] substantial documentation is required. Both animal testing and *in vitro* testing are covered by the ISO10993 series[6] that is comprised of 18 parts including general evaluation, animal welfare requirements, tests for DNA damage, interactions with blood components, etc. Several *in vivo* standards for medical device testing are also provided by the American Society for Testing and Materials; however, these are not integrated into European device testing regulations.

Advantages of standardisation
The ISO standards facilitate the use of replacement, reduction, and refinement in animal research, for example, by defining the minimum sample size for studies, and indicating where *in vitro* assays can be used instead. Together with the EU directives, the standards help to prevent poorly tested and potentially unsafe products from reaching the European market. The documentation of device testing required by ISO standards ensures accurate records of any testing procedures carried out. The ISO standards also remind researchers of good laboratory practices, such as labelling and traceability of samples; otherwise these common sense practices may not be implemented thoroughly.

The standardisation of research methods makes it easier to compare devices and the results of testing. The standards may also encourage the use of "gold standard"



techniques, rather than less effective methods. For example, with regard to the evaluation of local effects surrounding an implant, methods for quantitative scoring of soft tissue reactions by counting immune cell types within tissue sections are provided for by ISO10993-6;[6] researchers might otherwise evaluate the local effects by purely qualitative means. Standards also provide a balance between the production of quality research and research that may be too time consuming or impractical.

Limitations of standardisation

Perhaps the main problem with ISO standards is that they can become quickly outdated – especially as there is a time lag between the validation and implementation of a new ISO standard. As such, important testing methods may be overlooked. For example, analysis of animal tissues could include quantitative polymerase chain reaction (qPCR), a technique considered a gold standard for quantifying gene expression.[7] Furthermore qPCR requires very little tissue, is relatively fast, and reliable if designed properly. Reliance on an outdated ISO standard may prevent quality research from being carried out if institutions work to meet the ISO recommendations rather than design their own, more extensive investigations. ISO standards may not always be compatible with the unique aspects of a study, or be too general to be fit for purpose. The standards sometimes lack detail, leaving room for interpretation – meaning that experimental methods may differ between labs and make comparison of results difficult, defeating the main purpose of standardisation. For example, ISO 10993-11[8] states that there is no absolute criterion for selecting a particular animal species for systemic toxicity testing of medical devices. Similarly, with regard to the microscopic evaluation of tissue samples surrounding an implant material described in ISO10993-6, the types and amounts of tissues to be harvested and subsequent details of tissue processing is unspecified. The scoring systems offer no guidance on how to distinguish the different cell types – for example, whether cells should be labelled with chemical markers, or simply analysed by morphology.

Lastly, institutions may not afford to purchase access to standards, and uncertified institutions lacking the funds for ISO accreditation or the equivalent, may be penalised despite producing good research. Similarly, certified institutions are seen to have attained a "badge of quality" and so may be held to less scrutiny. However, ISO standard compliance does not remove the possibility of poor work being carried out, since departures from ISO standards may not be recognised and experimental errors may not be apparent from documentation.

Standardisation in other areas of preclinical device testing

Other areas of preclinical testing may benefit from more up-to-date and informative ISOs; for example ISO14242 on the wear of total hip joint prostheses has a 2012 version, which was revised in 2014, with some evidence of improvement in clinical outcomes.[9] In contrast to the *in vivo* modelling, ISO10993 includes many more specific test parameters for *in vitro* testing. Complete cell toxicity protocols are contained in ISO 10993-5 detailing specific cell lines, time points and reagents to be used; for example the use of BALB/c 3T3 cells for the Neutral Red Uptake cell toxicity test.[10] This may be a reflection of the relative ease of standardising a simpler test system such as cultured cells, versus entire animals with complex tissue structures and numerous cell types.

Conclusions

Validated and standardised methods for testing various aspects of the use of an implantable medical device are as important as for pharmaceuticals. While the ISO-recommended tests are in place, for *in vivo* testing they need to be updated or replaced with newer methods to increase the reliability of medical device testing. Once validated, these tests need to be adapted to the specificities of the given device.

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