

Animal welfare and ISO – the International Organisation for Standardization

Jon Richmond

Home Office, UK

Corresponding author: Dr. Jon Richmond

Home Office: PO Box 6779, Dundee, DD1 9WN, United Kingdom

Phone: +(44)-1382-223189, jon.richmond@homeoffice.gsi.gov.uk

Abstract

The International Organisation for Standardization (ISO) is a world-wide federation of national standards bodies. The work of preparing International Standards is carried out through ISO Technical Committees composed of national experts and in collaboration with international organisations both governmental and non-governmental. The 10993 series of ISO standards deal with the biological safety of medical devices and materials, and provide one means of satisfying regulatory requirements with respect to their biological safety. Although risk assessments must be undertaken on case-by-case basis, these standards establish essential requirements relating to the selection and performance of test methods, including animal tests. ISO Standard 10993-2 sets out the animal welfare provisions to be satisfied if compliance with the 10993 series of standards is to be established and, as the only animal welfare standard produced by ISO, it has also become a normative reference in other ISO standards describing animal use. The last revision of ISO Standard 10993-2 was completed in July 2006, and makes good contemporary provision for the welfare of animals used for biological testing. This paper reviews both the processes and product of this last revision, and commends specific components of the process as good examples where international agreement and collaboration has enabled the production, publication and adoption of a document that takes full account of the 3Rs.

Keywords: 3Rs, ISO, reduction, refinement, replacement

Introduction

The effective implementation of the 3Rs and the benefits they bring in terms of animal welfare, quality of science and the resulting societal benefits requires action not only at local and national level but, most importantly, at international level. Only timely changes in scientific and regulatory practice at international level allow these gains to be fully realised.

One important, although little known to many scientists in the context of the 3Rs, example of international co-operation that can be said to have made a difference has been the production of an International Standard on animal welfare by the International Organisation for Standardization (ISO). Produced as one of a series of International Standards on the biocompatibility of medical devices and materials, it has since become a normative standard, a set of essential requirements, within a large range of International Standards relating to healthcare products.

ISO

The International Organisation for Standardization is commonly referred to as ISO: not an acronym, but from the Greek word "isos" meaning equal.

ISO (Anon. 1) is a non-Governmental organisation: a federation of 157 national standards bodies, dedicated to developing and maintaining International Standards applicable to wide range of goods, processes and services – from clocks and watches to replacement heart valves. The agreed and published International Standards produced by ISO are recognised not only within the 157 countries of the federation, but in many other countries as well.

There are three main categories of ISO members: member bodies, corresponding members, and subscription members – with much of the technical work being undertaken by the member bodies.

Standards work is done through a range of Technical Committees (TCs) which develop, review and maintain over 16,000 standards. The detailed work is undertaken within over 3,000 Working Groups (WGs), and involves over 50,000 experts world-wide.

These experts are nominated by the individual national standards bodies and comprise both Government and non-Government organisation experts.

The ISO processes, depending on the quality of the available scientific evidence and the need for common standards, produce a range of agreed outputs including International Standards, technical reports, technical specifications, publicly available specifications, technical corrigenda, and guides.

National standards bodies

National standards bodies prepare and publish national standards in addition to contributing to supra-national standards work at regional and international level. As standards are developed national standards are superseded by regional standards, and regional standards are superseded by international standards. For example a UK national standard produced by the British Standards Institute is superseded by the equivalent European (CEN) standard, which in turn is superseded by the equivalent International (ISO) Standard.

What are standards?

Although they do not themselves constitute free-standing regulations or requirements, standards are commonly cited in legislation as one way of establishing compliance with certain regulatory requirements.

ISO standards define and set authoritative, publicly available, common, objective, agreed and mutually recognised standards for which there is an international need for a common technical specification and are therefore relevant to materials, procedures and products which are traded internationally.

They represent the current, agreed, state-of-the-art, publicly available, authoritative technical consensus. They may cover product and performance specifications; codes of practice; management systems; test methods and strategies; and measurement, sampling and analysis. They are periodically reviewed both to ensure that there is still a demand for a commonly agreed technical reference, and that the published material has kept pace with technological and regulatory progress.

What are they used for?

International Standards facilitate design and manufacture: manufacturers know what the required product technical specifications are and how their products and processes must interface with other products and processes.

They establish internationally accepted safety and performance criteria: properties of importance to manufacturers, purchasers and consumers.

They provide consistency, quality and economies

by allowing direct comparisons to be drawn between competing products in the knowledge, notwithstanding other individual merits and unique selling points, that products conforming to the standard are of the same minimum quality with respect to defined technical, performance and safety criteria. Thus they inspire confidence in manufacturers, regulators, purchasers, providers, users and consumers.

Although as free-standing documents the use of International Standards is strictly voluntary rather than compulsory, they are commonly cited in legislation (typically as one means of demonstrating compliance and satisfying the regulatory requirements): they are referenced in contracts including those covering public-sector procurement (as a straight-forward means of specifying essential technical, performance and safety criteria); they form the basis of many internationally recognised quality management systems (as the benchmark for product certification): and, because of their status and relevance, are also referenced in marketing material.

The 10993 series of international standards

The 10993 series of ISO standards (Anon. 2) deal with an important and specific component of healthcare biological safety: the biocompatibility of medical devices and materials. Separate ISO standards (referred to as 'vertical' standards) deal with other aspects of design and performance for a wide range of medical devices. A medical device is a healthcare product, whether used for diagnostic, prophylactic or therapeutic use, that produces its benefits by other than pharmacological or immunological means.

As a risk-based material, product and use specific safety assessment is required, the 10993 series does not prescribe fixed testing packages or the pass/fail criteria to be applied to materials in all circumstances – in some devices no risks are acceptable, in other circumstances a degree of risk may be both acceptable and inevitable. As such the standards are intended to be understood, interpreted and used by experts – as flexibility, judgment and justification are required to determine the preferred testing strategy and methods. The resulting risk assessments and decision making processes must be undertaken on a case-by-case basis.

Within a risk-management framework the 10993 series of International Standards identify the range of biocompatibility properties that may be relevant, and when and how these properties should be characterised and evaluated. They contain provisions relevant to test methods and testing strategies, and are one way to demonstrate compliance with a diverse range of national and international regulatory requirements relating to the biocompatibility of medical devices. Table 1 lists the 19 ISO standards that currently comprise the 10993 series.

Table 1: The 10993 Series of ISO Standards

- Evaluation and testing
- Animal welfare
- Genotoxicity, carcinogenicity, reproductive toxicology
- Interactions with blood
- In vitro cytotoxicity
- Implantation
- Ethylene oxide residues
- Degradation products
- Irritation/sensitisation
- Systemic toxicity
- Sample preparation and reference materials
- Degradation - polymers
- Degradation - ceramics
- Degradation - metals
- Toxicokinetics
- Allowable limits
- Chemical characterisation
- Physicochemistry
- Immunotoxicology

How ISO standards are developed

International Standards are only developed when ISO members are agreed that there is a need for them and that they will be used in practice.

Any ISO member body can propose that a new standard is created, or that an existing standard is revised. These "new work item proposals (NWIP)" are then put out for ballot by all member bodies. If there is sufficient support for the NWIP the task will be assigned to an appropriate ISO TC, and the background work and preparation undertaken by an appropriately constituted ISO WG (Anon. 3).

According to a fixed timetable the TC must then prepare and publish a committee draft (CD) setting out the emerging proposals. Again this is put out to ballot and, again if there is support, it is further developed as a draft international standard (DIS): which in turn is put out to ballot and there is support it is redrafted as a final draft international standard (FDIS). Each round of balloting permits member bodies to submit editorial and/or technical comments for consideration with a view to ensuring there is international consensus and support for the final agreed standard. The FDIS, taking account of any comments received, is then subjected to ballot and, if there is sufficient support, an agreed international standard is published.

The structure of an international standard

The agreed structure for an international standard is shown at Table 2.

Normative references comprise other essential requirements that must be demonstrably satisfied when claiming compliance with the standard. The power of the 10993 standard relating to animal welfare is not simply that is applicable to the

Table 2: The Structure of an International Standard

- Foreword
- Scope
- Normative references
- Terms and Definitions
- Common provisions
- Test methods, general aspects
- Test Report
- Annexes
- Bibliography

biocompatibility testing of medical devices and materials: as it is the only ISO standard dealing with animal welfare it has also become a normative reference within the much wider range of ISO standards making reference to the use of animals for scientific purposes.

ISO 10993 – Part 2 – animal welfare requirements

The 10993 series of ISO standards deals with the biocompatibility testing and evaluation of medical devices and materials, and a number of the standards in the 10993 series make reference to animal test methods – both on their selection, and on their performance.

10992 Part 2, Animal Welfare Requirements (Anon. 4), contains essential requirements that such animal testing must satisfy. As mentioned above, in addition to being an essential requirement when claiming compliance with the 10993 series of standards, 10993-2 is also a normative reference within a much wider range of ISO standards.

The first edition of the 10993-2 standard was published in 1992, and full revised second edition, unanimously adopted by the ISO membership (when 75% approval would have been sufficient), was published in July 2006.

The first edition had little impact: it focused largely on general principles and aspirations, but contained few essential requirements that those using animals had to demonstrably satisfy. The revision was prompted by the realisation that in order to better promote scientific validity it was necessary to ensure better provision was made for animal welfare through a document setting out evidence-based essential requirements.

The revision process

The revision of ISO 10993-2 provides a good case-study of effective international co-operation and collaboration to produce an internationally recognised standard impacting world-wide on animal welfare in a wide domain of product development and regulatory testing.

The revision was undertaken by ISO TC194/WG3, of which I was convenor. The detailed technical work and drafting was undertaken by a team of 25 experts from 9 countries. At each stage on the process (CD,

Table 3: ISO Standard 10993 Part 2 Key Provisions

- ...promoting good science through paying proper regard to maximizing the use of scientifically sound non-animal tests and by ensuring that those animal performed to evaluate the biological properties of materials used in medical devices are conducted humanely according to recognized ethical and scientific principles.
- The application of such humane experimental techniques, including high standards of animal care and accommodation, both help to ensure the scientific validity of the safety testing and enhance the welfare of the animals used.
- ...specifies the minimum requirements to be satisfied to ensure and demonstrate that proper provision has been made for the welfare of animals used in tests to assess the biocompatibility of materials used in medical devices.
- Applies to tests performed on vertebrate animals other than man.
- Provides a framework for decision making
- Requires justification for animal use: the minimization of pain, suffering, distress or lasting harm, high standards of accommodation and care, competence of personnel
- Provisions relate to study design including test strategies, methods, animal numbers, species; sources and health-status of animals: re-use of animals; care, accommodation and use; humane endpoints; euthanasia

DIS and FDIS) all member bodies had the opportunity to offer both editorial and technical comments for consideration.

Within the Working Group, whilst a number of competing national preferences and individual moral stances were represented and were reflected in the comments received, national and personal agenda were declared and then set aside as the Group applied its collective technical expertise to developing an objective contemporary animal welfare standard.

The revised standard was prepared with the intention of ensuring and safeguarding scientific validity by requiring consistently high standards of animal care and welfare and application of the 3Rs. The most relevant key provisions are set out in Table 3.

Thus the published standard, ISO Standard 10993-2, sets out a 3R framework for decision making and practice requiring that animal use and study design are demonstrably justified; that any resulting pain, suffering, distress or lasting harm are minimised; and that recognised high standards of care and accommodation are the norm.

In developing this standard all of the experts involved sought to develop an evidenced-based

standard based on good contemporary practice, and to set aside their personal and national interests (they were nominated as technical experts not as national delegates). The Working Group conducted much of its business by e-mail, but met at least once a year for detailed technical discussions and editorial meetings including consideration of comments received from individual member bodies and other ISO Working Groups.

Its inclusion as a normative reference in a much wider range of ISO standards than the series within which it was prepared tends to reinforce the quality of the product as an evidence-based set of provisions where good animal welfare sets the scene with high-quality science. Thus ISO Standard 10993-2 has already impacted on a range of animal testing strategies and practices world-wide, promoting good science as a result in the development and evaluation of a range of healthcare products.

Lessons learned

This is a case where the successful output was the product of effective international co-operation, involving a wide-range of technical experts, and largely free of national or personal agenda.

The appointment of internationally recognised technical experts, from a range of backgrounds but participating as experts rather than national delegates, was essential to this success. It allowed the Working Group to apply its talents purely to the technical considerations free of ideological or political considerations.

The resulting consensus document (unanimously adopted with no negative votes cast) properly balances the legitimate needs of science and industry, largely in the context of patient safety, against the protection of animals from unnecessary use and suffering.

It is a contemporary document that is demonstrably fit for purpose as by promoting scientific validity in studies designed, undertaken and evaluated to promote patient safety for a wide range of healthcare products by requiring the most relevant and reliable test methods are selected and used in cases where animal use is justified, it makes proper provision for the care and use of the animals.

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