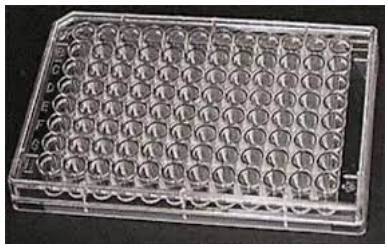

To Test or Not to Test: The Value of Biological Safety Testing
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Each year, thousands of tests are conducted on biomaterials to check whether they are biologically safe and suitable for use in medical devices. This article addresses the question of whether or not these tests are necessary, or in fact, useful.

Concerns about biological safety testing

In the recently published one-thousandth issue of Clinica,[1] a series of brief personal perspectives were provided by a number of people with long involvements with the medical technology sector. I took the opportunity to make a simple comment on the value of biological testing, stating that there are two problems with the procedures we use today to demonstrate that a material meets the criteria for adequate biological safety and gains regulatory approval. The first of these problems concerns the vast amount of repetitive testing that has to be done, which largely demonstrates facts that are already known. The second concerns the capability of current tests to predict clinical performance, or more importantly, to identify serious risks. In this article, these two problems are discussed and expanded.

Repetitive and unnecessary testing

My views on the first of these problems is colored by the masses of documentation I have seen and reviewed concerning legal arguments over the adequacy of biomaterials testing. This frequently arises when product liability or personal injury cases are brought to court, and each side tries to argue that the amount of preclinical testing performed on the device in question was either inadequate (for the plaintiff) or more than adequate (for the defense).
The number of mice, guinea pigs, hamsters and rats that have been used to assess the biological safety of the standard biomaterials used in medical devices such as titanium, silicone elastomers, polytetrafluoroethylene, polyurethane, polyethylene and carbon is huge, and one has to wonder whether it is justified. It is true that the standards for this testing require the materials to be in a form analogous to the way they are used in the device in question. Different processing routes can give rise to different types of surface, which can have their own subtle biocompatibility differences. It is also true that there can be some not-so-subtle changes in the formulation of well- known polymers, which alter the characteristics of leachables and, therefore, influence some biological responses. However, no new animal tests should be required to establish that a wide series of generic biomaterials have intrinsic biological safety, and it is hard to see in principle why this type of testing should continue. In practice, it is easy to see why manufacturers feel the need to conduct these tests: there is no

recognized database of validated and regulatory body approved biological safety reports to which they can refer. They may, if they are lucky, be able to refer to a Master File held by the supplier of the material, but legal responsibility comes back to them, and the material still has to be demonstrated "to be safe" under their conditions.

Unfortunately, this leads to defensive tactics and means that more and more tests are done. This would not be a problem if the results were meaningful, which brings us the second point.

The value of biological safety testing

Everyone working in this field is aware of the widely used ISO 10993 series of standards for the Biological Evaluation of Medical Devices. It is emphasized here that these represent a carefully worked out set of tests, which, during the course of their development, have followed current thinking and state-of-the-art experimentation of biomaterials and toxicity. As such, they cannot be faulted as a logical evolutionary series of tests. One has to say, however, that it is extremely difficult to evaluate a portfolio of data derived from these tests and produce a clear, objective risk analysis relating to biological performance. This is primarily because the data is usually qualitative or semi-quantitative and open to interpretation. Often with a portfolio of this type it is possible to be ultra cautious and determine that a material is not biologically safe. Yet, at the same time, one could be practical and use common sense and determine that there is no significant risk. Both approaches have equal validity.

Many of the tests involve extraction processes, whereby samples of the material are exposed to one or more solvents or media into which any potentially leachable or extractable component is transferred. The extract is then tested on cell lines for cytotoxicity or in vitro mutagenicity, or on animals for sensitization, irritation in vivo mutagenicity and so on. The validity of the test is obviously predicated on the suitability of the extraction media to produce the clinically relevant amount of extraction. Because this will vary from one situation to another and is essentially an unknown, their value has to be questioned. Furthermore, in each case, a description of the observations made on cells and/or on animals and some measurement, usually a subjective scoring system, constitute the report, and it is a matter of judgement as to whether the results are significant or not. The compiler of the report and the assessor at the regulatory body have to give judgement on whether an observation of a slight oedema in one out of three animals used for the sensitization test, compared to no oedema in the other two, is of any significance.

The same reservations can be made about all types of test that are in use. With the implantation of materials in animals there are also the questions of biological variability and surgical technique, which, even taking into account the use of controls, means that subjective assessments of the cellular response are difficult to interpret. The number of times one can read of the presence of macrophages, foreign body giant cells and lymphocytes in a histological report and then see the conclusion that there was no inflammation still surprises me.

Clinical predictiveness

One of the most challenging aspects of biological safety testing is that we do not really know if it is of any value, the main reason for this being the confidentiality of much of the data. There is a certain amount of evidence to demonstrate that biological

safety testing does not prevent major medical device problems. Many devices, and especially but not exclusively, implantable devices, have failed because of adverse responses from the patient, ranging from anaphylactic shock to thromboembolic events and granulomas; but these risks were not picked up in the preclinical regulatory testing, nor anticipated by those responsible for regulatory approval. What we do not know is the number of devices or materials that have failed biological safety testing and never seen the light of day because of this. This could be a good thing if the test failures really did represent a clinical risk, or a bad thing if the test failure had nothing to do with clinical risk and a potentially useful product was withheld from clinical practice.

This discussion reminds us yet again that neither cells nor animals are really adequate surrogates for human patients for determining the host response to medical devices. Manufacturers have to protect themselves by complying with the recognized standards for testing, and patient groups no doubt will continue to demand that the products they receive are as safe as possible. Both positions are reasonable and defendable. The problem is that our current system is not really protecting either group.

At some stage in the future, and this may not be far off, modelling and computational processes may supersede the current rather crude form of testing. In the meantime, a much closer look at risk analyses based on detailed examination of all relevant literature, and a system for the release under controlled conditions of test data that is currently confidential, would be beneficial to form a much larger and relevant database.

Reference

1. Clinica, 1000, p. 2, 18 March 2002