Alternatives to the Animal Testing of Medical Devices

The Report and Recommendations of ECVAM Workshop 17\textsuperscript{1,2}

Ove Svendsen,\textsuperscript{3} Bernward Garthoff,\textsuperscript{4} Horst Spielmann,\textsuperscript{5} Arne Hensten-Pettersen,\textsuperscript{6} Jørn C. Jensen,\textsuperscript{3} Marja R. Kuijpers,\textsuperscript{7} Roland Leimgruber,\textsuperscript{8} Manfred Liebsch,\textsuperscript{5} Wolfgang G.K. Müller-Lierheim,\textsuperscript{9} Gun Rydhög,\textsuperscript{10} Ursula G. Sauer,\textsuperscript{11} Gottfried Schmalz,\textsuperscript{12} Bushra Sim\textsuperscript{13} and Susanna Stea\textsuperscript{14}

\textsuperscript{3}Scantox, 36A Hestehavevej, Ejby, 4623 Lille Skensved, Denmark; \textsuperscript{4}Bayer AG, PF Centre Monheim, 51368 Leverkusen, Germany; \textsuperscript{5}ZEBET, BgVV, Dierdersdorfer Weg 1, 12277 Berlin, Germany; \textsuperscript{6}Nordisk Institut for Odontologisk Materialprøvning (NIOM), Kirkeveien 71B, 1344 Haslum, Norway; \textsuperscript{7}National Institute of Public Health and the Environment (RIVM), 3720 BA Bilthoven, The Netherlands; \textsuperscript{8}RCC Registration and Consulting Company, 4452 Itingen/Basel, Switzerland; \textsuperscript{9}mdl medical device testing, Dr Müller-Lierheim GmbH, Krautstrasse 2, 87700 Memmingen, Germany; \textsuperscript{10}Gambro Lundia AB, Magistratsvägen 16, 220 10 Lund, Sweden; \textsuperscript{11}Akademie für Tierschutz, Spechtstrasse 1, 85579 Neubiberg, Germany; \textsuperscript{12}Department of Operative Dentistry and Periodontology, University of Regensburg, Franz-Josef-Strauss-Allee 11, 93042 Regensburg, Germany; \textsuperscript{13}Department of Human Morphology, University of Nottingham Medical School, Queen’s Medical Centre, Nottingham NG7 2UH, UK; \textsuperscript{14}Laboratory for Biocompatibility Research on Implant Materials, Istituto Rizzoli, Via di Barbaro 1/10, 40136 Bologna, Italy

Preface

This is the report of the seventeenth of a series of workshops organised by the European Centre for the Validation of Alternative Methods (ECVAM). ECVAM’s main goal, as defined in 1993 by its Scientific Advisory Committee, is to promote the scientific and regulatory acceptance of alternative methods which are of importance to the biosciences and which reduce, refine or replace the use of laboratory animals. One of the first priorities set by ECVAM was the implementation of procedures which would enable it to become well-informed about the state-of-the-art of non-animal test development and validation, and the potential for the possible incorporation of alternative tests into regulatory procedures. It was decided that this would be best achieved by the organisation of ECVAM workshops on specific topics, at which small groups of invited experts would review the current status of various types of \textit{in vitro} tests and their potential uses, and make recommendations about the best ways forward (1).

The workshop on Alternatives to the Animal Testing of Medical Devices was held in Vaeloese, Copenhagen, Denmark on 24–26 November 1995, under the chairmanship of Ove Svendsen (Scantox, Denmark). The workshop was organised by the chairman, with the help of Bernward Garthoff (Bayer AG, Germany), Horst Spielmann (ZEBET,
Germany) and Coenraad Hendriksen (RIVM, The Netherlands), all of whom are members of the ECVAM Scientific Advisory Committee. The aims of the workshop were to determine the current status of medical device testing and to outline future directions in this area, especially in relation to the Medical Device Directive, Directive 93/42/EEC (2). In particular, possibilities for reducing the current use of laboratory animals, and for promoting the use of alternative methods for testing medical devices, were discussed. The toxicological studies recommended in Part 1 (Guidance on Selection of Tests) of the standards series ISO 10993 and EN 30993 (3, 4), drawn up by the International Organisation for Standardisation (ISO) and the European Committee for Standardisation (CEN), respectively, were critically evaluated. The workshop participants were representatives of industry, research institutes, national organisations, regulatory agencies and the animal welfare community. Their conclusions and recommendations are summarised in the final section of this report.

Introduction

Medical devices comprise an extremely heterogeneous category of materials. According to Directive 93/42/EEC (2), “medical device” means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for humans for the purpose of: a) diagnosis, prevention, monitoring, treatment or alleviation of disease; b) diagnosis, monitoring, treatment, alleviation of or compensation for any injury or handicap; c) investigation, replacement or modification of the anatomy or of a physiological process; or d) control of conception, and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means. Thus, “medical devices” include, for example, dental materials, intra-uterine devices, and hip and knee joint replacement prostheses (5). An estimated 400,000 different items are covered by Directive 93/42/EEC (2).

Advances in technological processes for the production of various types of materials have opened up many possibilities for the development of new, or improved, medical devices. Since the number of elderly people throughout the world will continue to rise for the foreseeable future, it is likely that there will be a concomitant increase in the demand for biomaterials and biomedical devices. Polymers may be used successfully for the manufacture of implants, medical devices and dental products. Metals have mainly been employed in the production of implants to be used in hard tissues. The new ceramics, composites and biological materials open up many possibilities for the development of medical devices. The combination of developments in the fields of materials technology, biotechnology and medicine may revolutionise the production of medical devices in the future.

In the normal course of biomedical applications, medical devices can be in direct or indirect contact with the patient. The potential hazards of the device to the patient depend upon the conditions and duration of contact with it. Manufacturers are obliged to establish the safety of their products before they are marketed. Thus, preclinical assessments of the toxic potentials of medical devices are typically undertaken, to determine any possible hazards which may be associated with their use.

The regulations governing the manufacture and sale of medical devices varied greatly between countries until recently (3–10). However, from 1 January 1995, medical devices to be marketed in the European Union (EU) must comply with the regulations described in Directive 93/42/EEC, the Medical Device Directive (2). Similar requirements exist with respect to the marketing of medical devices in the United States. On 1 May 1995, the Food and Drug Administration (FDA) switched from following the requirements detailed in the Tripartite Document of 1986 (11) to those given in ISO 10993 (3).

Standards for medical devices

Standards are prepared by technical committees (TC); those concerning the safety of medical devices are prepared at the ISO level by ISO TC 194, and at the CEN level by CEN TC 206. The European standards EN 30993 are currently being developed on the basis of the corresponding international standards, ISO 10993 (3, 4). The various parts of the
ISO and CEN standards for the safety testing of medical devices are shown in Table I; parts 1–7 and 9–12 have been published, while the remaining parts are still being prepared. Future parts will deal with other relevant aspects of biological testing.

Conformity assessment

The assessment of safety is based on the fulfillment of “essential requirements” (as detailed in Directive 93/42/EEC [2]) which cover all aspects of the device. They include biological properties, and chemical and physical behaviour, microbial contamination, and environmental properties. Medical devices which conform to these requirements receive the CE (conformity assessment) mark (5). Within the EU, all medical devices must carry the CE mark from 14 June 1998; this should ensure that comprehensive documentation is available which demonstrates the safety of the device. The documentation for biocompatibility usually includes results from toxicological studies conducted in animals as well as results from human clinical studies. The CE mark can be given by the manufacturer or by a “Notified Body” (administrative bodies which are currently being established). There are a variety of procedures for which the CE mark can be obtained, which are described in detail in the annexes to the Directive (2). These include full quality assurance, EC-type examination, production quality assurance, product quality assurance, and self-certification by declaration of conformity.

ISO and CEN Guidance on Selection of Tests for the Biological Evaluation of Medical Devices

The ISO 10993-1/EN 30993-1 standard (3, 4) provides guidance on the selection of tests for the biological evaluation of medical devices. The international and European standard advocates a structured assessment

Table I: International standards (ISO 10993/EN 30993) for testing the biological properties of medical devices (3, 4)

<table>
<thead>
<tr>
<th>Part</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Guidance on selection of tests</td>
</tr>
<tr>
<td>2.</td>
<td>Animal welfare requirements</td>
</tr>
<tr>
<td>3.</td>
<td>Tests for genotoxicity, carcinogenicity and reproductive toxicity</td>
</tr>
<tr>
<td>4.</td>
<td>Selection of tests for interactions with blood</td>
</tr>
<tr>
<td>5.</td>
<td>Tests for cytotoxicity: <em>in vitro</em> methods</td>
</tr>
<tr>
<td>6.</td>
<td>Tests for local effects after implantation</td>
</tr>
<tr>
<td>7.</td>
<td>Ethylene oxide sterilisation residuals</td>
</tr>
<tr>
<td>8.</td>
<td>Clinical investigation</td>
</tr>
<tr>
<td>9.</td>
<td>Degradation of materials related to biological testing</td>
</tr>
<tr>
<td>10.</td>
<td>Tests for irritation and sensitisation</td>
</tr>
<tr>
<td>11.</td>
<td>Tests for systemic toxicity</td>
</tr>
<tr>
<td>12.</td>
<td>Sample preparation and reference materials</td>
</tr>
<tr>
<td>13.</td>
<td>Identification and quantification of degradation products from polymers</td>
</tr>
<tr>
<td>14.</td>
<td>Identification and quantification of degradation products from ceramics</td>
</tr>
<tr>
<td>15.</td>
<td>Identification and quantification of degradation products from coated and uncoated metals and alloys</td>
</tr>
<tr>
<td>16.</td>
<td>General guidance on toxicokinetic study for degradation products and leachables</td>
</tr>
<tr>
<td>17.</td>
<td>Glutaraldehyde and formaldehyde residues in industrially sterilised medical devices</td>
</tr>
</tbody>
</table>
of medical devices, including consideration of all of the information and data available on starting materials, processing aids, human use history, etc., thereby minimising the requirements for additional testing. However, it has become apparent that ISO 10993-1/EN 30993-1 is subject to misinterpretation. Therefore, it is recommended that:

1. ISO 10993-1/EN 30993-1 should be revised to improve the clarity of the rationale for the standard.

2. The *Introduction* should contain a statement to the effect that the standard intends to provide a strategy for avoiding unnecessary testing, use of animals, and human and financial resources, without compromising the safety of medical devices.

3. The sub-title of the standard should be reworded to read “Guidance on Safety Assessment and Selection of Tests”.

4. The scope of the standard should be more clearly defined, to make it obvious that it: a) only covers aspects of biological safety, and not the performances of individual devices, which are covered in vertical standards; and b) only applies to the evaluation of new devices, not to regular batch control testing during the production of medical devices.

5. Detailed guidance should be provided in Clause 4 of the standard, on the steps to be undertaken during the biological safety evaluation process. This should relate to: a) the collection of all information available on the materials used in the production of the device, and on its application (see clauses 4.1, 4.2 and 6.1 of the current standard); b) the identification of any potential biological hazards by consideration of device/tissue/body fluid interfaces, diffusible leachables (distinguishing local and systemic effects), release of viscous substances, release of wear particles, and degradation, resorption and biotransformation; c) determination of the potential hazards which need to be addressed by additional testing, taking into account all relevant experience and information available about the device and its constituent materials. It is recommended that any additional testing which is deemed necessary is conducted in the following sequence: i) physical and chemical testing of both new and aged materials; ii) *in vitro* tests; and iii) *in vivo* tests; d) evaluation of the risks associated with the potential hazards identified during testing; and e) evaluation of the safety of the device (risk assessment), with weighing of any risks against the probable benefits of using the device.

6. A flow chart should be provided as an annex, which details the decisions to be taken during the biological evaluation process (such a flow chart is outlined in Figure 1).

**Implementation of the Medical Device Directive in Europe**

According to the Medical Device Directive, *Directive 93/42/EEC* (2), a product meets the defined safety requirements if it has been tested by methods described in either harmonised standards or in the European Pharmacopoeia. Article 5 of the Directive refers to compliance with harmonised standards as being a suitable manner for fulfilling the “essential requirements” laid down in Article 3. Thus, to comply with the “essential requirements” of the Directive, European harmonised standards may be used. The term “harmonised” refers to a special procedure for developing such standards, according to rules established by the EU (5). The procedure comprises recognition of the standard and its publication in the *Official Journal of the European Communities*. It is the policy of CEN to adopt ISO standards whenever possible, or to have parallel voting for newly developed standards.

The workshop participants recognised the importance of harmonised standards. It is recommended that the process for preparing European standards should be continued and speeded up, since the availability of harmonised standards is a prerequisite for rational decision making concerning the identification of those tests which are appropriate for particular medical devices, and for the subsequent conduct of the relevant tests.

The ISO 10993-1/EN 30993-1 standard (3, 4) describes safety testing procedures which should be considered for all medical devices; they are referred to as “horizontal” harmonised standards. “Vertical” harmonised standards relate to specific applica-
Figure 1: Flow chart showing the decisions to be taken when selecting tests appropriate for the biological evaluation of medical devices

- Is there direct or indirect body contact? No
- Yes
  - Is there a similar device in clinical use? Yes
  - No
  - Evaluate the device for potential hazards
  - Decide which tests are to be performed
  - Perform the necessary tests
  - Evaluate the differences compared with the existing device: are new hazards involved? Yes
  - No
  - Undertake risk/benefit analysis
  - Is the device identical in all aspects to the existing device? Yes
  - No testing required

It is recommended that:

1. The European Commission should be asked to harmonise as quickly as possible all parts of the horizontal standards EN 30993 (4) and prEN-ISO/DIS 7405 (Dentistry: Preclinical Evaluation of Biocompatibility of Medical Devices Used in Dentistry: Test Methods [16, 17]), and all vertical standards.

2. The European Commission should be asked to ensure that procedures for implementing the requirements of Directive 93/42/EEC are identical in all of the EU Member States.

Conclusions of particular medical devices; for example, the localised effects produced by hip prostheses (5). To date, only parts 3, 4, 5 and 6 of the horizontal standard EN 30993 (4) have been harmonised, and are cited in the Official Journal of the European Communities. In addition, several vertical standards for testing medical devices have not yet been harmonised. As a consequence, from 1 January 1995 in Germany all animal tests on medical devices (such as those laid down in DIN 58 360 [12], DIN 58 361 [13], DIN 58 363 [14] and DIN 58 367 [15]) are defined as “experiments”, and these have to be authorised individually by the state governments.
Conformity Assessment of Existing Products

Directive 93/42/EEC (2) outlines an approach for ensuring that existing products are not "over-tested" with respect to fulfilling regulatory requirements. Similarly, this is emphasised in the Notified Bodies Group Draft Document, NBM/026/95, in which alternative ways of demonstrating compliance with the "essential requirements" detailed in Directive 93/42/EEC are outlined.

For the safety evaluation of medical devices which are already in clinical use, the workshop participants were of the opinion that any animal testing should be avoided, since appropriate clinical data could be presented instead. Due to the large number of different medical devices in existence, it is virtually impossible to formalise the procedure for evaluating the clinical data which are submitted. Decisions can only be taken on a case-by-case basis by expert committees. It is proposed that the Notified Bodies should take decisions about the appropriateness of the clinical data presented.

Occasionally, there may be reasons for doubting the quality of the clinical data. Nevertheless, any animal testing should be strictly limited to those instances where the clinical data are insufficient to provide reasonable assurance that the product meets the "essential requirements" given in Directive 93/42/EEC (2).

Unpublished Toxicological Data

It is assumed that the major proportion of all toxicological information is not published in scientific journals, but is contained in archives/databases in the industrial companies which conducted/financed the testing. The main reasons for not publishing toxicological data are: a) protection of the products from imitation (patents, etc.); and b) protection of the investment made in actually conducting the required testing. Duplication of animal testing could be prevented if all of the unpublished data were to be made available. Under the Freedom of Information Act in the USA, unpublished data are made available following the registration of a chemical or product; considerable efforts are being made to implement a similar system in other countries.

It is recommended that ECVAM should organise a workshop to discuss ways in which industry could be encouraged to provide animal data, while at the same time fully protecting their own interests.

ISO 10993-2: Animal Welfare Requirements

There has been an unacceptable delay in the transposition of ISO 10993-2 (Animal Welfare Requirements) to the equivalent European standard, EN 30993-2. In 1992, during the first CEN vote on the acceptance of ISO 10993-2, France, the UK and The Netherlands voted against its acceptance. The British commented that Part 2 was not necessary, since there was a national law covering animal welfare; the French commented that Part 2 contradicted Directive 86/609/EEC (18); and The Netherlands commented on various editorial points. The French and British comments were rejected during a CEN discussion in April 1993, and it was decided to again put forward Part 2 of ISO 10993 for adoption as a European standard.

During the initial enquiry, France and the UK voted against accepting Part 2 as a European standard, their arguments being the same as during the first CEN vote in 1992. However, if put to the necessary formal final vote, ISO 10993-2 would be accepted as a European standard. To date, the procedure for the formal final vote has

Raw Materials Used in the Manufacture of Medical Devices

Many of the raw materials which are used in the manufacture of medical devices have been tested with respect to their use for certain applications, and have been found to have acceptable properties. A list of these substances, including their known uses, should be published, since this could: a) speed up the validation process; b) prevent unnecessary animal tests from being conducted; and c) save time and money. It is recommended that ECVAM should organise a workshop, or establish a working group, to define guidelines for the establishment of a "Generally Recognised As Safe" (GRAS) list of raw materials used in the production of medical devices.
not been launched; the reason for this is not known.

The workshop participants agreed that there was an urgent need to accept ISO 10933-2 as the CEN standard, EN 30993-2. All recent EU Directives which refer to animal testing mention the requirements of Directive 86/609/EEC (18), except for the Medical Device Directive, Directive 93/42/EEC (2). This is probably because Directive 93/42/EEC does not actually describe the animal tests required, but rather refers to “harmonised standards”. Consequently, the basic horizontal standard for all medical devices (EN 30993) should include a part relating to animal welfare.

It is recommended that:

1. ECVAM should exert its political influence to ensure the adoption of prEN 30993-2 as a harmonised European standard, which is applicable to all EU Member States.

2. Whenever animal tests have to be performed, the least sentient species possible should be selected. For example, for the pulp and dentine usage assessment, the pulp capping and pulpotomy test referred to in prEN-ISO/DIS 7405 should be used (17, 19, 20).

Medical Devices and Alternatives to Animal Tests

The animal tests relevant to medical and dental materials and devices (2–4, 6–8, 11) can be divided into two categories: a) those used frequently; and b) those used rarely (Table II).

Acute systemic toxicity

The acute systemic toxicity test is considered to be of very little importance for the safety assessment of insoluble medical devices, since such materials leach only minute amounts of their constituents and these very seldom reach levels which cause any acute effects (21, 22). For other types of devices which are partly soluble or can disintegrate (for example, hydrocolloidal wound dressings), the outcome of the test is generally systemic collapse of the animals due to the viscosity, particulate nature, or other physical aspects of the extract/solution. Nevertheless, it is recognised that the test may be relevant for certain materials.

Abnormal toxicity

In addition to preclinical testing for acute systemic toxicity, some of the vertical standards also require that post-marketing tests for abnormal toxicity are conducted regularly, on a batch-by-batch basis. The test for abnormal toxicity is essentially the same as the acute systemic toxicity test.

The following standards require that the abnormal toxicity test is undertaken for both premarket testing and post-market batch testing: a) DIN 58 361 (Transfusion Containers and Accessories [12]); b) DIN 58 362 (Infusion Equipment and Accessories [13]); c) DIN 58 363 (Infusion Containers and

<table>
<thead>
<tr>
<th>Animal test</th>
<th>Frequently used</th>
<th>Rarely used</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute systemic toxicity</td>
<td></td>
<td>pyrogenicity</td>
</tr>
<tr>
<td>abnormal toxicity</td>
<td></td>
<td>haemocompatibility</td>
</tr>
<tr>
<td>skin irritation</td>
<td></td>
<td>oral, rectal, penile and vaginal mucosa</td>
</tr>
<tr>
<td>intracutaneous irritation</td>
<td></td>
<td>(mucous membrane) irritation</td>
</tr>
<tr>
<td>implantation toxicity</td>
<td></td>
<td>sub-chronic toxicity</td>
</tr>
<tr>
<td>sensitisation</td>
<td></td>
<td>chronic toxicity</td>
</tr>
<tr>
<td>eye irritation</td>
<td></td>
<td>reproductive toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>carcinogenicity</td>
</tr>
</tbody>
</table>
Accessories [14]); and d) DIN 58 367 (Transfusion, Infusion, Injection, Elastomeric Parts [15]). For the devices referred to in a), b) and c), both aqueous and oily extracts have to be applied to ten mice per group, by either intravenous (aqueous extracts) or intraperitoneal (oily extracts) injection, at an application volume of 50ml/kg body weight. The effects are then compared to those observed in ten control mice (with separate controls for each of the two groups; that is, 40 mice in total). For the medical devices referred to in d), aqueous extracts have to be injected into mice intravenously, at 100ml/kg body weight, within a fixed administration time of 2 minutes. The mice are then observed for 14 days.

In contrast, monographs of the German Pharmacopoeia for the same types of medical devices either do not require the abnormal toxicity test, or the procedure given is different from the procedures described in equivalent national standards (for example, different numbers of animals should be used; control groups are not needed; and the observation period is 24 hours).

Batch testing for abnormal toxicity is generally considered to be totally unnecessary for most solid plastic materials, since there is a long history of negative test results. In the rare cases where the test has given positive results, these were due to neglect of the standard rinsing procedures or to artefacts of extract application (predominantly when oil was given intraperitoneally at 50ml/kg body weight).

It is recommended that the requirement for the abnormal toxicity test to be conducted on batches should be deleted in all standards harmonised in accordance with Directive 93/42/EEC. Medical devices produced in compliance with Good Manufacturing Practice should not result in unexpected systemic toxicity. Any failures in cleaning procedures, etc. could easily be detected by using simple cytotoxicity tests.

**Skin irritation**

The validation of alternative methods for predicting skin irritation for various types of test materials other than medical devices (for example, industrial chemicals and cosmetics) is in progress. For chemicals, data from skin irritation testing *in vitro* correlate well with those obtained in *in vivo* irritation tests. The use of human skin cultures is one of the most promising developments (23). Nevertheless, at present the *in vivo* skin irritation test would seem to be relevant for medical devices.

It is recommended that ECVAM should assign high priority to organising a validation study on *in vitro* methods for the dermal irritancy testing of medical devices. DGXII (Directorate General for Science, Research and Development) should be asked to provide funding for the development of reference materials for the validation study. Experts from Notified Bodies established under Directive 93/42/EEC and/or experts on the safety testing of medical devices should be consulted during the design, management and evaluation of the study.

**Intracutaneous irritation**

The intracutaneous irritation test in rabbits has been part of the basic safety evaluation battery of tests for many years. It was developed to simulate the intracutaneous irritation which can occur in humans upon exposure of breached skin to a foreign irritating device, or when the device is introduced subcutaneously. The method measures erythema and other skin reactions, and is widely used for evaluating the primary tissue responses to a device. ISO 10993 has referenced the intracutaneous irritation test as a commonly recommended safety evaluation test method. Nevertheless, for certain types of medical devices, the test does not provide any substantial information about the safety of the device itself (21, 22).

It is recommended that manufacturers of solid devices and/or devices which will not be in contact with the skin, should not consider this test to be relevant for safety evaluation purposes, and therefore they should not conduct the test. However, the test may be relevant for wound dressings and similar devices which may be in long-term contact with breached skin.

**Implantation toxicity**

The implantation tests described in the ISO standard have been refined compared with those given in the US Pharmacopoeia. For medical devices for which long-term implantation is envisaged, the animal test would appear to be warranted (24). The possibility of using alternative methods for assessing
short-term implantation toxicity should be addressed (25, 26).

Sensitisation

Due to the very complex mechanisms involved in skin sensitisation, no alternative test can be suggested as a replacement for the current method, the Magnusson & Kligman guinea-pig maximisation test. The Buehler test, which involves only topical application, is considered to be markedly less sensitive than the maximisation test, and should therefore be avoided.

Eye irritation

The Draize eye irritation test is the procedure of choice if biomaterials have to be evaluated for biocompatibility with the eye. In most cases, it is sufficient to test extracts of solid materials.

Pyrogenicity

The Limulus amoebocyte lysate (LAL) test for detecting the presence of endotoxins would appear to be sufficient for low release purposes for most medical devices. However, there are cases when a pyrogenic effect would not be detected with the LAL test (for example, with devices based on biological materials); in such circumstances, the rabbit pyrogenicity test should be used.

Haemocompatibility

Since haemocompatibility is recognised as being extremely species-specific, animal models are of questionable relevance. The risk of haemolysis can easily be evaluated by using in vitro methods, although it is recognised that cytotoxicity tests are much more sensitive than the animal procedures.

Mucous membrane irritation

In accordance with international standards for the safety testing of medical devices, dental materials and certain other devices have to be tested for their biocompatibility with mucous membranes by undertaking acute and other short-term studies (27). Animal mucous membrane tests are considered to be of little value because of their poorly developed status, whereas cell and tissue culture methods have been shown to be useful for such assessments (28).

Mucous membrane tests on vagina, penis and rectum are listed in the ISO standard, but they are not considered to be standardised tests which should be conducted routinely. Various scientists expressed their concern about such testing during the drafting of ISO 10993, and standards for these tests were therefore omitted.

It is recommended that ECVAM should support a validation study on in vitro tests for assessing the mucous membrane biocompatibility of dental materials. DGXII should be asked to provide funding for the development of reference materials for the study. The design, management and evaluation of the validation study should be carried out in close cooperation with experts on the safety testing of medical devices.

Long-term toxic effects

With respect to long-term toxicity tests, such as those for determining sub-chronic, chronic, reproductive and carcinogenic effects, no alternative methods can be recommended as replacements for the animal tests. Results of in vitro mutagenicity tests would, in most cases, provide a good indication of possible carcinogenic effects, but such tests are only considered to be appropriate as screens for mutagenicity. The need to conduct long-term tests should be determined on a case-by-case basis.

Conclusions and Recommendations

Implementation of the Medical Device Directive in Europe

1. The European Commission should be asked to insist that all parts of the horizontal standards, EN 30993 and prEN-ISO/DIS 7405, and all vertical standards dealing with the biological evaluation of medical devices, are harmonised as quickly as possible.

2. The European Commission should be asked to ensure that procedures for implementing the requirements of Directive 93/42/EEC are identical in all EU Member States.

Conformity assessment of existing products

3. For the safety evaluation of medical devices already in clinical use, all animal
testing should be avoided and appropriate clinical data should be presented instead (preferably to the Notified Bodies).

Raw materials used in the manufacture of medical devices

4. ECVAM should organise a workshop, or establish a working group, to define guidelines for the establishment of a “Generally Recognised As Safe” (GRAS) list of raw materials used in the production of medical devices.

Unpublished toxicological data

5. ECVAM should organise a workshop to discuss ways in which industry could be encouraged to provide unpublished toxicological data on medical devices, while at the same time fully protecting their own interests.

ISO 10993-2: animal welfare requirements

6. ECVAM should exert its political influence to ensure the adoption of prEN 30993-2 as a harmonised European standard which is applicable to all EU Member States.

7. Whenever animal tests have to be performed, the least sentient species possible should be selected.

Medical devices: alternatives to animal tests

8. The requirement for the abnormal toxicity test to be conducted on batches should be deleted in all standards harmonised in accordance with Directive 93/42/EEC. Medical devices produced in compliance with Good Manufacturing Practice should not result in unexpected systemic toxicity.

9. Manufacturers of medical devices which will not be in contact with the skin should not consider the intracutaneous irritation test to be relevant for safety evaluation purposes, and therefore they should not conduct the test. However, the test may be relevant for wound dressings and similar devices which may be in long-term contact with breached skin.

10. ECVAM should assign high priority to organising a validation study on in vitro methods for the skin irritation testing of medical devices.

11. ECVAM should support a validation study on in vitro tests for assessing the mucous membrane biocompatibility of dental materials.

References

15. Anon. (1986). DIN 58 367, Teil 1: Transfusion,


