BIOCOMPATIBILITY OF MEDICAL DEVICES

ISO 10993

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WHAT IS MEDICAL DEVICE?

Any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article, **intended by the manufacturer to be used**, alone or in combination, for human beings for one or more of the **specific purpose(s)** of:

diagnosis, prevention, monitoring, treatment or alleviation of disease or an injury, investigation, replacement, modification, or support of the anatomy or of a physiological process, supporting or sustaining life, disinfection of medical devices, and which

**does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means,**

but may be assisted in its function by such means
DEFINITION

Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the device with the body.

- Do not produce adverse mechanical and/or biological, local or systemic effects
- Leachable or degradation products are not carcinogenic
- No adverse effect on biological systems (reproductive, immune, nerve etc.) and/or developmental effects
# BLUE BOOK MEMORANDUM (G95-1) May 1, 1995

<table>
<thead>
<tr>
<th>Device Categories</th>
<th>Biological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cyotoxicity</td>
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<tr>
<td><strong>Body Contact</strong></td>
<td></td>
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<tr>
<td>Skin</td>
<td>A</td>
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<td></td>
<td>B</td>
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<tr>
<td></td>
<td>C</td>
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<tr>
<td>Mucosal membrane</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Breached or compromised surfaces</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td><strong>Surface devices</strong></td>
<td></td>
</tr>
<tr>
<td>Blood path, indirect</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Tissue/bone/dentin communicating+</td>
<td>A</td>
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<tr>
<td></td>
<td>B</td>
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<tr>
<td></td>
<td>C</td>
</tr>
<tr>
<td>Circulating blood</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
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<tr>
<td></td>
<td>C</td>
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<tr>
<td><strong>Implant devices</strong></td>
<td></td>
</tr>
<tr>
<td>Tissue/bone</td>
<td>A</td>
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<td></td>
<td>B</td>
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<td></td>
<td>C</td>
</tr>
<tr>
<td>Blood</td>
<td>A</td>
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<td></td>
<td>B</td>
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<td></td>
<td>C</td>
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</tbody>
</table>

## Contact duration:
A- Limited (24h)
B- Prolonged (24h to 30 days)
C- Permanent (>30days)

## Additional Test to be considered:
- Chronic Toxicity
- Carcinogenicity
- Reproductive & Development
- Biodegradable

X = ISO Evaluation Tests for Consideration
O = Additional Tests which may be applicable
Note + Tissue includes tissue fluids and subcutaneous spaces
Note ^ For all devices used in extracorporeal circuits
INTERNATIONAL STANDARDS

ISO 10993
Biological evaluation of medical devices

ISO 14971
Medical devices - Application of risk management to medical devices
NATIONAL STANDARDS

ASTM / ASTM International
American Society for Testing and Materials

ANSI
American National Standards Institute

AAMI
American National Standards Institute

BSI
British Standards

DIN
German Institute for Standardization

A joint effort by standards development organizations AAMI, ANSI, ASTM, and DIN created a single, centralized database for medical device standards.
The ISO 10993 Guideline covers only the testing of materials and devices that come into direct or indirect contact with the patient's body.

With the exception of Products which might be considered to be medical devices but for which there is not yet a harmonized approach, are:

1. aids for disabled/handicapped people;
2. devices for the treatment/diagnosis of diseases and injuries in animals;
3. accessories for medical devices;
4. devices incorporating animal and human tissues, which might meet the requirements of the above definition but are subject to different controls.
ISO 10993 GUIDELINE

Biological Evaluation of Medical Devices

- Part 1: Evaluation and testing within a risk management process
- Part 2: Animal welfare requirements
- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- Part 4: Selection of tests for interactions with blood
- Part 5: Tests for in vitro cytotoxicity
- Part 6: Tests for local effects after implantation
- Part 7: Ethylene oxide sterilization residuals
- Part 9: Framework for identification and quantification of potential degradation products
- Part 10: Tests for irritation and skin sensitization
- Part 11: Tests for systemic toxicity
- Part 12: Sample preparation and reference materials
- Part 13: Identification and quantification of degradation products from polymeric medical devices
- Part 14: Identification and quantification of degradation products from ceramics
- Part 15: Identification and quantification of degradation products from metals and alloys
- Part 16: Toxicokinetic study design for degradation products and leachables
- Part 17: Establishment of allowable limits for leachable substances
- Part 18: Chemical characterization of materials
- Part 19: Physico-chemical, morphological and topographical characterization of materials
- Part 20: Principles and methods for immunotoxicology testing of medical devices
IMPORTANT

This part of ISO 10993 is intended for use by professionals, appropriately qualified by training and experience, who are able to interpret its requirements and judge the outcome of the evaluation for each medical device, taking into consideration all the factors relevant to the device, its intended use and the current knowledge of the medical device provided by review of the scientific literature and previous clinical experience.
Assessment of the biological safety of the medical device starts with:

- Evaluation of existing relevant data from all sources
- Any history of clinical use or human exposure data
- Any existing toxicology and other biological safety data on product and component materials, breakdown products and metabolites
- Identification of gaps in the available data set on the basis of a risk analysis
Identification of additional data necessary to analyze the biological safety of the device

The physical and chemical characteristics of the various candidate materials

In assessing the relevance of data, on prior use of a material, to the biological evaluation, the level of confidence in the historical data should be taken into account
MATERIAL CHARACTERIZATION

Material characterization is a crucial first step in the biological evaluation process.

In the selection of materials to be used in device manufacture, the first consideration shall be *fitness for purpose* with regard to characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological and mechanical properties.
The extent of required chemical characterization depends on what pre-clinical and clinical safety and toxicological data exist, and on the nature and duration of body contact with the medical device

but as a minimum

The characterization shall address the constituent chemicals of the device and possible residual process aids or additives used in its manufacture
The identity and quantity of novel materials and chemicals present should be established or measured.

For devices that have known leachable chemical mixtures, potential synergies of the leachable chemicals should be considered.

Where the potential for degradation exists under the conditions of manufacture, sterilization, transport, storage, and use of the device, the presence and nature of degradation products shall be characterized.
Testing shall be performed on the sterile final product, or representative samples from the final product or materials processed in the same manner as the final product (including sterilization).
SELECTION OF A REPRESENTATIVE SAMPLE

If a device cannot be tested as a whole, each individual material in the final product shall be represented proportionally in the test sample.

The test sample of devices with surface coatings shall include both coating material and the substrate, even if the substrate has no tissue contact.

The test sample shall include a representative portion of the joint and/or seal if adhesives, radio frequency (RF) seals, or solvent seals are used in the manufacture of a portion of the device which contacts patients.

When different materials are present in a single device, the potential for synergies and interactions shall be considered in the choice of test sample.

The test sample shall be chosen to maximize the exposure of the test system to the components of a device that are known to have potential for a biological response.
EXTRACT PREPARATION

The extraction vehicles and conditions of extraction used shall be appropriate to the nature and use of the final product and to the purpose of the test

a) $(37 \pm 1) \, ^\circ C$ for $(72 \pm 2) \, h$;
b) $(50 \pm 2) \, ^\circ C$ for $(72 \pm 2) \, h$;
c) $(70 \pm 2) \, ^\circ C$ for $(24 \pm 2) \, h$;
d) $(121 \pm 2) \, ^\circ C$ for $(1 \pm 0,1) \, h$.

The increased temperature may cause cross-linking and/or polymerization of the polymer and, therefore, decrease the amount of free monomer that is available to migrate from the polymer.

The increased temperature could cause degradation products to form that are not typically found in the finished device under conditions of use.
## SAMPLE SIZE

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Extraction ratio (surface area or mass/volume) ± 10 %</th>
<th>Examples of forms of materials</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5 mm</td>
<td>6 cm²/ml</td>
<td>film, sheet, tubing wall</td>
</tr>
<tr>
<td>0.5 to 1.0 mm</td>
<td>3 cm²/ml</td>
<td>tubing wall, slab, small moulded items</td>
</tr>
<tr>
<td>&gt; 1.0 mm</td>
<td>3 cm²/ml</td>
<td>larger moulded items</td>
</tr>
<tr>
<td>&gt; 1.0 mm</td>
<td>1.25 cm²/ml</td>
<td>elastomeric closures</td>
</tr>
<tr>
<td>Irregularly shaped solid devices</td>
<td>0.2 g sample/ml</td>
<td>powder, pellets, foam, non-absorbent moulded items</td>
</tr>
<tr>
<td>Irregularly shaped porous devices (low density materials)</td>
<td>0.1 g/ml</td>
<td>membranes</td>
</tr>
</tbody>
</table>

**NOTE** While there are no standardized methods available at present for testing absorbents and hydrocolloids, the following is a suggested protocol.

Determine the volume of extraction vehicle that each 0.1 g or 1.0 cm² of material absorbs. Then, in performing the material extraction, add this additional volume to each 0.1 g or 1.0 cm² in an extraction mixture.

Area includes the combined area of both sides of the sample
BIOLOGICAL EVALUATION TESTS

All tests shall be conducted according to recognized current/valid best laboratory/quality practices, for example Good Laboratory Practice (GLP) or ISO/IEC 17025 and the data shall be evaluated by competent, informed professionals.
Biocompatibility studies

GLP implementation

Non-Clinical Studies

MEDICAL DEVICE
QUALITY SYSTEMS

General

Quality systems intended to assure production of quality products

“suitable for the customer”

Good Laboratory Practice

Specific Quality System imposed by the authorities when public health is involved

Non-clinical safety studies
MAIN GLP GUIDELINES

**OECD Principles of GLP**

No 1: OECD Principals on Good Laboratory Practice

**FDA CFR Code of Federal Regulations Title 21**

PART 58 Good Laboratory Practice for Non-clinical Laboratory Studies

**EPA US Environmental Protection Agency**

Good Laboratory Practices Standards

40 CFR part 160 FIFRA Federal Insecticide, Fungicide, and Rodenticide Act

40 CFR part 792 TSCA Toxic Substances Control Act
OECD – GLP

Areas of Expertise

1. Physical-chemical testing
2. Toxicity studies
3. Mutagenicity studies
4. Environmental toxicity studies on aquatic and terrestrial organisms
5. Studies on behavior in water, soil and air; Bioaccumulation
6. Residue studies
7. Studies on effects on mesocosms and natural ecosystems
8. Analytical and clinical chemistry testing
9. Other studies
OECD DEFINITIONS

The purpose of the Principles of Good Laboratory Practice is to **promote the development of quality test data.**

The Principles of GLP should be applied to the non-clinical safety testing of test items contained in pharmaceutical products, pesticide products, cosmetic products, veterinary drugs, food additives, feed additives, and industrial chemicals. The purpose of testing these test items is to obtain data on their properties and/or their safety with respect to human health and/or the environment.
Good Laboratory Practice (GLP) is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are:

- Planned
- Performed
- Monitored
- Recorded
- Reported
- Archived
MILESTONES

RESOURCES

Manpower; Facility; equipment

REGULATIONS

Standard Operating Procedures

CHARACTERIZATION

Test materials; Reference materials

DOCUMENTATION

On-line recording; Final Report; Archiving

CONTROL SYSTEM

Quality Assurance Department
Management commitment

Each test facility management should ensure that these Principles of Good Laboratory Practice are complied with, in its testing facility.

Appointment of Study Director

Ensure that a sufficient number of qualified and trained personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the study.
A test facility should have written Standard Operating Procedures approved by Test Facility Management and Quality Assurance that are intended to ensure the quality and integrity of the data generated by that test facility.

Deviations from Standard Operating Procedures related to the study should be documented.
CHARACTERIZATION

Test Item/Test Device is any product that has to be evaluated and is the reason for the conduct of the Study

Each Test and Reference Items should be appropriately identified

- Mean of Identification / composition / purity
- Expiry date
- Storage conditions
- Safety data
- Disposal
For each study, a written Study Plan should exist prior to the initiation of the study

All data generated during the study should be recorded directly, promptly, accurately and legibly

A Final Report should be issued for each Study

**Storage (Archiving)**

- Study plan, raw data, samples & specimens, and the final report of each study
- All QA inspections performed by the Quality Assurance Programme
- Records of qualifications, training, experience and job descriptions of personnel
- Records and reports of the maintenance and calibration of apparatus
The testing facility should have a documented Quality Assurance Programme to assure that studies performed are in compliance with the Principles of Good Laboratory Practice.

Verify that the Study Plan and Study Report contains the information required for compliance with the Principles of Good Laboratory Practice and Regulatory Requirements.

Conduct inspections to assure that the studies are comply with the Principles of Good Laboratory Practice and conducted according to the Study Plan & Standard Operating Procedure.
CHECKLIST

1. GLP accreditation
2. Management commitment
3. Qualified Personnel – Training Records
4. Quality Assurance Department
5. Adequate Facility
6. Availability of Calibrated equipment
7. Controlled and certified reagents
8. known and controlled source of Test System (in-vivo / in-vitro)
9. Formulation Department
10. Archiving
USE ONLY CERTIFIED LABORATORY

GLP like
Based on GLP
According to GLP
In the spirit of GLP
Etc......
Thank you

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Oded laor