Institute for Industrial Research & Toxicology
औद्योगिक अनुसंधान एवं विष विज्ञान संस्थान

BIOCOMPATIBILITY TESTING OF MEDICAL DEVICES (ISO 10993)

IIRT- Ghaziabad, UP, (India)

- **Accreditation with CPCSEA (Ministry of Environment & Forest), Government of India.**
- **Accreditation with ISO 9001:2008 (Provision of Industrial Research & Analysis Services)**
- **Accreditation with OHSAS 18001:2007 (Provision of Industrial Research & Analysis Services)**
- **OECD Principles of Good Laboratory Practices endorsed by European GLP Monitoring Authority (viz., UK)**
- **Food safety & Drug Administration, Government of Uttar Pradesh**
- **NABL (National Accreditation Board for Testing & Calibration Laboratories)**

Biocompatibility Studies for Medical Devices under ISO 10993 and USP Plastics

Cytotoxicity	Implantation Testing	Genotoxicity	Irritation	Systemic Toxicity
➢ Agar overlay		➢ AMES test	Intracutaneous reactivity	Acute, Sub-acute and Pyrogen test
➢ MEM Elution	**Intramuscular (USP/ISO) and subcutaneous Implantation**	➢ Mouse lymphoma	Dermal Irritation	
➢ Direct contact		➢ In vitro and In vivo micro nucleus	Ocular Irritation	Sub-chronic and Chronic
➢ MTT assay		➢ Chromosome Aberration	Mucosa Irritation	
➢ Colony Formation			(Oral, Rectal, Vaginal, Penile)	Reproduction toxicity

SENSITIZATION	SYSTEMIC TOXICITY	HEMO-COMPATIBILITY	USP PLASTICS
➢ Maximization Test	➢ Acute, Sub-acute and Pyrogen test	➢ ASTM Hemolysis tests – Direct and Indirect contact	➢ USP I-IV
➢ Closed Patch (Buehler)			➢ Systemic injection
➢ Local lymph node assay	➢ Sub-chronic and Chronic		➢ Intracutaneous test
	➢ Reproduction toxicity		➢ Implant test

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TEST DETAILS AND SAMPLE REQUIREMENT

Category	Test Name	Surface area	Powder	Liquid	TAT
			G	Ml	(Week)
Cytotoxicity	Agar Overlay MEM Elution Direct Contact MTT Assay Colony Formation	1 x 4 pieces 65 cm^2 65 cm^2 65 cm^2 65 cm^2	5	20	4
Sensitization	Murine LLNA Maximization Test Closed Patch Test	N/A 2 60 cm x 6 devices 2 1 in x 130 devices	16 24 60	30 60 80	5 7 8

Irritation	Intra-cutaneous Test Dermal Irritation Ocular Irritation Mucous membrane Irritation	60 cm x 2 devices 2 60 cm x 2 devices 2 60 cm x 2 devices Varies	8 4 2 Varies	40 10 5 varies	5 5 5 Varies

LIST OF STANDARDS FOR BIOCOMPATIBILITY TESTS

S.No	Standards	Title	Description
1	ISO 10993	Biocompatibility	This standard gives the basic guidelines of biocompatibility
2	ISO 10993-1:2009	Evaluation and testing in the risk of management process	-The general principle governing the biological evaluation of medical devices within a risk management process; - The general categorization of devices based on the nature and duration of their contact with the body; -The evaluation of exiting relevant data from all sources; -The identification of gaps in the available data set on the basis of a risk analysis; -The identification of additional data sets necessary to analyze the biological safety of the medical device; -The assessment of the biological safety of the medical device;
3	ISO 10993-2	Animal welfare requirements	The standard specifies the minimum requirements to be satisfied to ensure and demonstrate that proper provision has been made for the welfare of animals used in animal tests to assess the biocompatibility of materials used in medical devices.
4	ISO 10993-3	Tests for genotoxicity, carcinogenicity and reproductive toxicity	The standard specifies strategies for hazard identification and tests on medical devices for the following biological aspects: genotoxicity, carcinogenicity, and reproductive and developmental toxicity
5	ISO 10993-4	Selections of tests for interactions with blood	The standard provide general requirement for evaluation the intersections of medical devices with blood. It describes: -A classification of medical and dental devices that are intended for use in contact with blood, based on the intended use and duration of contact as defined in ISO 10993-1;

			-The fundamental principle governing the evaluation of the interaction of devices with blood; **-The rationale for structured selection of tests according to specific categories, together with the principle and scientific basis of these tests.** **Detailed requirements for testing cannot be specified because of limitations in the knowledge and precision of tests for interactions of devices with blood. ISO 10993- 4:2002 describes biological evaluation in general terms and may not necessarily provide sufficient guidance for tests methods for a specific device.**
6	**ISO 10993-5**	**Tests for in vitro Cytocompatibility evaluation**	**The standard describes test methods to assess the in vitro Cytocompatibility evaluation of medical devices. These methods specify the incubation of cultures cells in contact with a device and/or extracts of a device either directly or through diffusion.** **These methods are designed to determine the biological response of mammalian cells in vitro using appropriate parameters.**
7	**ISO 10993-6**	**Tests for local effects after implantation**	**The standard specifies tests methods for the assessment of the local effects after implantation of biomaterials intended for use in medical devices.** **ISO 10993-6:2007 applies to materials that are** **- Solid and non-biodegradable;** **- Degradable and/or reserbable;** **- Non-solid, such as porous materials, liquids, pastes and particulates.** **ISO 10993-6:2007 may also be applied to medical devices that are intended to be used topically in clinical indications where the surface or lining may have been breached, in order to evaluate local tissue responses.**
8	**ISO 10993-7**	**Ethylene oxide sterilization residuals**	**The standard specifies allowable limits for residual ethylene oxide (EO) and ethylene chlorohydrin (ECH) in individual EO-sterilized medical devices, procedures for the measurement of EO and ECH, and methods for determining compliance so that devices may be released. Additional background, including guidance and a flowchart showing how the standard is applied are also included in informative annexes. EO-sterilized devices that**

			have no patient contact (e.g., in vitro diagnostic devices) are not covered by ISO 10993-7:2008.
9	ISO 10993-8	Selection of reference materials	The standard gives guidance on selection and qualification of reference materials for biological test (usually sent by the client).
10	ISO 10993-9	Framework for identification and quantification of potential degradation products	The standard provides general principle for the systematic evaluation of the potential and observed biodegradation of medical devices and for the design and performance of biodegradation studies. ISO 10993-9: 2008 consider both non- resorbable and resorbable materials
11	ISO 10993-10	Tests for irritation and delayed-type hypersensitivity	The standard describes the procedure for the assessment of medical devices and their constituent materials with regard to their potential to produce irritation and skin sensitization. ISO 10993-10:2010 includes: -Pretest considerations for irritation in silico and in vitro methods for dermal exposure; -Details of in vivo (irritation and sensitization) test procedures; -Key factors for the interpretation of the results. Instructions are given for the preparation of materials specifically in relation to the above tests and several special irritation tests are described for application of medical devices in areas other than skin.
12	ISO 10993-11	Tests for systemic toxicity	The standard specifies requirements and gives on the procedures to be followed in the preparation of samples and the selection of reference materials for medical device testing in biological systems in accordance with one or more parts of ISO 10993. Specifically, ISO 10993-12:2012 addressers the following: - Test sample selection; -Selection of representative portions from a device; -Test sample preparation; -Experimental controls;
			The standard specifies requirements and gives on the procedures to be followed in the

13	ISO 10993-12	Sample preparation and reference materials	preparation of samples and the selection of reference materials for medical device testing in biological systems in accordance with one or more parts of ISO 10993. Specifically, ISO 10993-12:2012 addressers the following: -Test sample selection; -Selection of representative portions from a device; -Test sample preparation; -Experimental controls; -Selection of, and requirements for, reference materials; -Preparation of extracts. ISO 10993-12:2012 in not applicable to live cells, but can be relevant to the material or device components of combination products containing live cells.
14	ISO 10993-13	Identification and quantification of degradation products from polymeric medical devices	ISO 1099313:2010 provides general requirements for the design of tests in a simulated environment for identifying and quantifying degradation products from finished polymeric medical devices ready for clinical use.
15	ISO 10993-14	Identification and quantification of degradation products from ceramics	Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics
16	ISO 10993-15	Identification and quantification of degradation products from metals and alloys	Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys
17	ISO 10993-16	Toxicokinetic study design for degradation products and leachables	Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables
18	ISO 10993-17	Establishment of allowable limits for leachable substances	Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances
19	ISO 10993-18	Chemical characterization of materials	Biological evaluation of medical devices Part 18: Chemical characterization of materials
20	ISO 10993-19	Physicochemical,morpholo gical and topographical characterization of materials	Biological evaluation of medical devices Part 19: Physico-chemical, morphological and topographical characterization of materials
21	ISO 10993-20	Principles and methods for immunotoxicology testing of medical devices	Biological evaluation of medical devices Part 20: Principles and methods for immunotoxicology testing of medical devices