PD233: Design of Biomedical Devices and Systems

(Lecture-14 Biocompatibility & Biomaterials Testing)

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Biomaterials

- Non-viable materials used as or part of medical device to perform a medical/biological function

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- Biomaterial : Any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used at any period of time as a whole or in part of a system which treats, augments or place any tissue, organ or function of the body.

-Boretos and Eden, 1984

- Examples:
  - Gold used for over 2000 year for dental implants
  - Wooden or ivory denture in middle ages
  - Metal bone plates and joint replacement early 1900s
  - Metallic alloys
  - Ceramics
  - Polymeric materials

How to test biomaterials for compatibility?

- Apart from the functional role for of the device, device material should not, either directly or through the release of their material constituents:
  - Produce adverse local or systemic effects
  - Be carcinogenic
  - Produce adverse reproductive and developmental effects
- For selecting appropriate tests, one must consider the ***chemical characteristics of device materials*** and the ***nature, degree, frequency, and duration*** of its exposure to the body

In general, the tests include

- Acutes
- Subchronic and chronic toxicity
- Irritation to skin, eyes, and mucosal surfaces
- Sensitization
- Hemocompatibility
- Genotoxicity
- Carcinogenicity
- Effects on reproduction including developmental effects

Additionally, depending on varying characteristics, intended use, and nature of contact, additional test may be required.
E.g.

a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb CSF

ISO 10993

- International Standards Organization (ISO), in an effort to harmonize biocompatibility testing, developed a standard for biological evaluation of medical devices documented in ISO 10993
- 12-part standard to evaluate the effects of medical device materials on the body
- The first part of this standard, ***Biological Evaluation of Medical Devices: Part 1: Evaluation and Testing***, provides guidance for selecting the tests to evaluate the biological response to medical devices.
- Other parts of the ISO standard deal with appropriate methods to conduct the biological tests suggested in Part 1 of the standard
- Please note US-FDA requires more testing than mentioned in ISO10993 in some places.

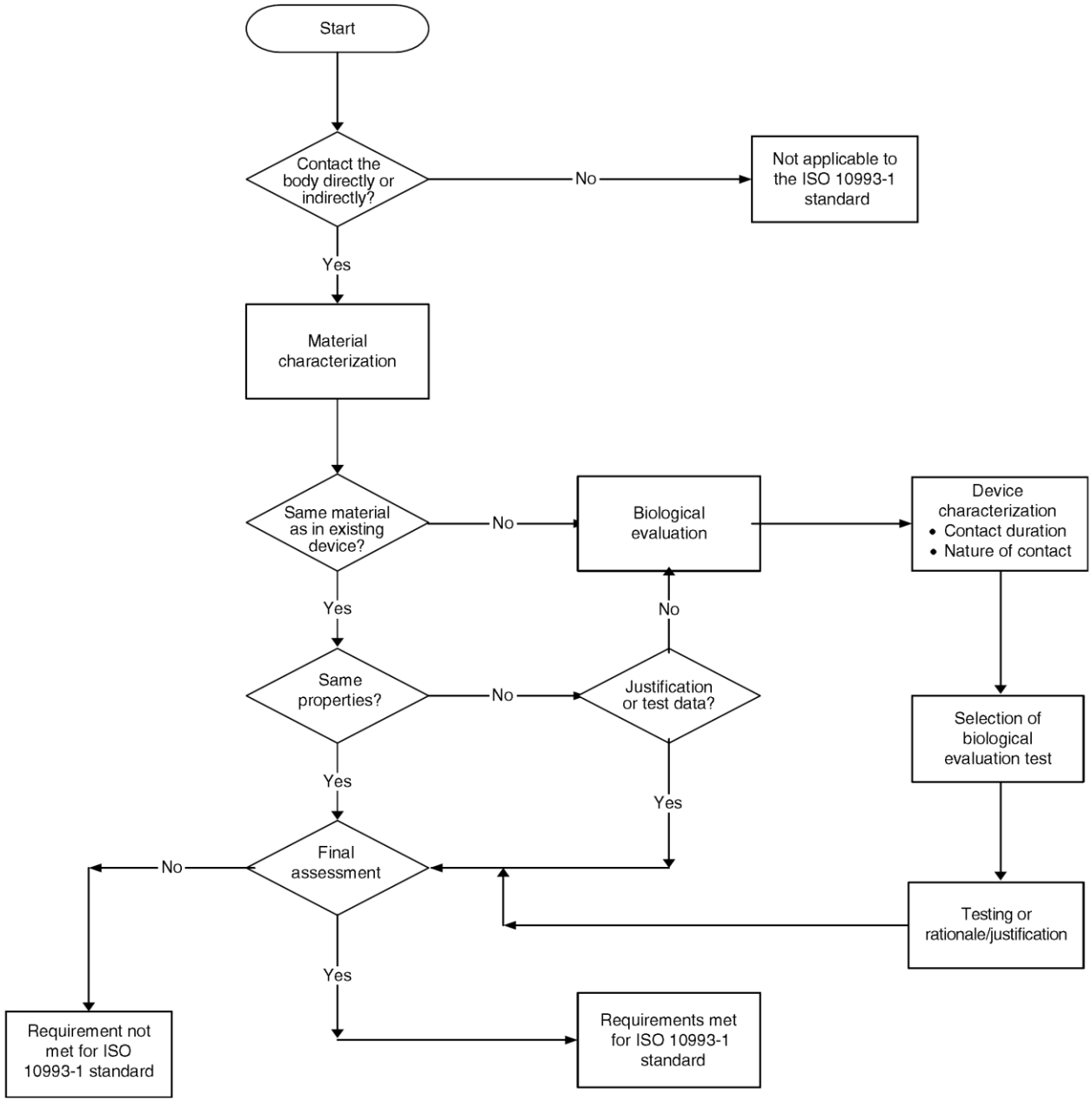

FIGURE 11.1 Steps in the biological evaluation of medical devices.

TABLE 11.1
Initial Evaluation Tests for Consideration

Device Categories	Body Contact	Contact Duration	Biological Effect: Cytotoxicity	Sensitization	Irritation	System Toxicity	Subchronic Toxicity	Geno-Toxicity	Implantation	Hemocompatibility
Surface devices	Skin	A	X	X	X	—	—	—	—	—
		B	X	X	X	—	—	—	—	—
		C	X	X	X	—	—	—	—	—
	Mucosal membrane	A	X	X	X	—	—	—	—	—
		B	X	X	X	O	O	—	O	—
		C	X	X	X	O	X	X	O	—
	Breached or compromised surfaces	A	X	X	X	O	—	—	—	—
		B	X	X	X	O	O	—	O	—
		C	X	X	X	O	X	X	O	—
External communicating devices	Blood path, indirect	A	X	X	X	X	—	—	—	X
		B	X	X	X	X	O	—	—	X
		C	X	X	O	X	X	X	O	X
	Tissue/bone/dentin communicating	A	X	X	X	O	—	—	—	—
		B	X	X	O	O	O	X	X	—
		C	X	X	O	O	O	X	X	—
	Circulating blood	A	X	X	X	X	—	O	—	X
		B	X	X	X	X	O	X	O	X
		C	X	X	X	X	X	X	O	X
Implant devices	Tissue/bone	A	X	X	X	X	O	—	—	—
		B	X	X	O	O	O	X	X	—
		C	X	X	O	O	O	X	X	—
	Blood	A	X	X	X	X	—	—	X	X
		B	X	X	X	X	O	X	X	X
		C	X	X	X	X	X	X	X	X

Notes: X is the ISO evaluation tests for consideration, O is the additional tests that may be applicable; A: 24 h, B: 24 h–30 days, C: >30 days.

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TABLE 11.2
Supplementary Evaluation Tests for Consideration

Device Categories	Body Contact	Contact Duration	Biological Effects: Chronic Toxicity	Carcinogenicity	Reproductive Development	Biodegradable
Surface devices	Skin	A	—	—	—	—
		B	—	—	—	—
		C	—	—	—	—
	Mucosal membrane	A	—	—	—	—
		B	—	—	—	—
		C	O	—	—	—
	Breached or compromised surfaces	A	—	—	—	—
		B	—	—	—	—
		C	O	—	—	—
External communicating devices	Blood path, indirect	A	—	—	—	—
		B	—	—	—	—
		C	X	X	—	—
	Tissue/bone/dentin communicating	A	—	—	—	—
		B	—	—	—	—
		C	O	X	—	—
	Circulating blood	A	—	—	—	—
		B	—	—	—	—
		C	X	X	—	—
Implant devices	Tissue/bone	A	—	—	—	—
		B	—	—	—	—
		C	X	X	—	—
	Blood	A	—	—	—	—
		B	—	—	—	—
		C	X	X	—	—

Notes: X is the ISO evaluation tests for consideration, O is the additional tests that may be applicable; A: 24 h, B: 24 h–30 days, C: >30 days.

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TABLE 11.3
Listing of Individual Parts of ISO 10993

Part	Title
1	Evaluation and testing
2	Animal welfare requirements
3	Tests for genotoxicity, carcinogenicity, and reproductive toxicity
4	Selection of tests for interactions with blood
5	Tests for cytotoxicity—in vitro methods
6	Tests for local effects after implantation
7	Ethylene oxide sterilization residuals
8	Clinical investigation of medical devices
9	Degradation of materials related to biological testing
10	Test for irritation and sensitization
11	Test for systemic toxicity
12	Sample preparation and reference material
13	Identification and quantification of degradation products from polymers
14	Identification and quantification of degradation products from ceramics
15	Identification and quantification of degradation products from coated and uncoated metals and alloys
16	Toxicokinetic study design for degradation products and leachables
17	Glutaraldehyde and formaldehyde residues in industrially sterilized medical devices

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ISO 10993-12 Preparations of Extracts

- Test should be carried out on representative sample of mass-produced device. It should be finished or treated in same way as mass produced device.
- Extracts are obtained various extraction media:
  - Physiological saline
  - Vegetable oil
  - Dimethylsulfoxide
  - Ethonol
  - Cell culture media (for cytotoxicity studies)

  Often at 37°C for 24-72 hour
- Amount of extraction media is normalize with respect to either surface area or mass of the device sample being used
  - 1.24 to 6 mm^2 per ml of extraction media
  - 0.1 to 0.2 gm per ml of extraction media

Cytotoxicity

- In-vitro test to test for potential ability of device to induce sub-lethal or lethal effect as observed at cellular level
- Three types cell culture based test are used:
  - Elution test
  - Direct contact test
  - Agar diffusion test

  Growth inhibition is used indicator for cytotoxicity

- These test are used as screening test for materials

Sensitization Test

- Sensitization refers to Allergic contact dermatitis where the reaction is caused of direct effect of the substance on the skin.
- Animal test typically using albino guinea pig

- Various phases of testing:
  - Induction phase
  - Resting phase
  - Challenge phase

Skin Irritation test (ISO 10993-10)

- Preferably tested in albino rabbits
- Done either with extracts or with directly the device

- Exposure for several hours to multiple days on intact skin
- Dermal irritation – reversible changes
- Dermal corrosion – irreversible changes

- Intracutaneous reactivity
  - To assess the localized reaction of tissue to leachable substances
  - Extract are administered as intracutaneous injections to rabbits
  - Undesirable intracutaneous reactivity includes redness or swelling
- Acute systemic toxicity
  - Required for all device categories that indicate blood contact
  - Adverse effect occurring within short span of administering the substance
  - Extracts of medical devices are usually administered intravenously or intraperitoneally in rabbits or mice

- Genotoxicity
  - To investigate materials for possible mutagenic effects, that is, damage to the body's genes or chromosomes
  - Required for all devices indicated for permanent skin contact (>30days) expect for surface devices with skin only contact
  - Can be carried out using bacteria or mammalian cell cultures
  - In some cases may be studied in-vivo as well in bone marrow or peripheral blood cells of rodents

- Implantation
  - Designed to assess any localized effects of a device designed to be used inside the human body
  - Performed in rabbits, with implantation being carried out in paravertebral muscles

- Hemocompatibity ISO-10993-4
  - To look for possible undesirable changes in the blood
  - Five categories of test
    1. Thrombosis
    2. Coagulation
    3. Platelets
    4. Hematology
    5. Immunology
- Subchronic and Chronic toxicity
  - Subchronic toxicity is the potentially adverse effect that can occur as a result of the repeated daily
  - Effect on target organs and the possibilities of toxin accumulation studied
  - one or two animal species are dosed daily, for 3-6 months

- Carcinogenicity
  - To observe test animals over a major portion of their life span to detect any development of neoplastic lesions (tumor induction) during or after exposure to various doses of a test substance.
  - In carcinogenicity studies, mice or rats are dosed every day for 18–24 months.
  - For medical device extracts, one dose level (again the highest practically applicable volume) is usually sufficient.
  - At the completion of the dosing period, all surviving animals are sacrificed and their organs and tissues examined microscopically for the presence of tumors.