ISO 10993

# General principles applying to biological evaluations of medical devices

* Structured biological evaluation programme with a risk management process
* Planned
* Carried out
* Documented by knowledgeable and experienced professionals
* Risk management to identify aspects of specific technical competencies and personel responsible
* Evaluate advantage and disadvantage of :
  + Physical and chemical characteristics
  + History of clinical use
  + Existing toxicology
  + Biological safety data
  + Breakdown product and metabolities
  + Study of preclinical and clinical experience and actual testing
  + No testing needed if material has history of safe use
* Selection:
  + Fitness for purpose with regards to characteristics and properties of material
  + Chemical
  + Toxicological
  + Physical
  + Electrical
  + Morphological
  + Mechanical properties
* Taken into account
  + Material of manufacture
  + Intended additives
  + Process contaminants
  + Residues
  + Leachable substance
  + Degradation products
  + Other components and interactions in the final product
  + Performance characteristic of the product
  + Physical characteristic: porosity, particle size shape and surface morphology
  + Identification of chemical constituents and consideration of chemical characterisation preceding biological testing
  + Physical effects of device if they impact the biocompatibility
  + For implants –systemic effects and local effects considered
* Choice of tests
* Data required in biological evaluation
* Conditions of exposure
* Nature
* Frequency
* Degree
* Duration of exposure
* All known possible biological hazards shall be taken into account
* Test results cannot guarantee freedom from potential biological hazards
* Biological investigation
* Carefull observation
* Unexpected adverse reaction
* Short term effects
  + Acute toxicity
  + Irritation to skin/eye/mucosal surface
  + Hemolysis
  + Thrombogenicity
  + Subchronic
  + Chronic toxic effects
  + Sensitization
  + Allergy
  + Genotoxicity
  + Carcinogenicity
  + Teratogenicity
* Selection of invitro invivo test shall be based on end user applications
* Re evaluated if:
  + Change in the source of material
  + Change in formulation, processing, primary packaging or sterilization of product
  + Change in manufacturerinstruction for storage change in shelf life and and or transport
  + Change in intended use
  + Evidence of adverse events
* Nature and mobility of chemical constituents

# Categorization of medical devices

* Nature and duration of body contact

## Body contact

### Skin

Contact intact skin surface only

Examples: electrodes, external prosthesis, fixation tapes,compression bandages

Monitors of various types

### Mucosal membrane

Contact intact mucosal membrane

Examples : contact lenses

* Urinary catheters
* Intravaginal and intra intestinal devices
* Stomach tubes
* Sigmoidoscopies
* Colonoscopies
* Gastroscopes
* Endotracheal tubes
* Bronchoscopes
* Dental prosthesis
* Orthodontic device

### Breached or compromised surfaces

* Dressing
* Healing devices
* Occlusive patches

## External communicating device

### Blood path, indirect

Contact blood path in one point and serve as conduit for entry into vascular system

* Solution administration sets
* Extension sets
* Transfer sets
* Blood administration sets

### Tissue bone dentin

Contact tissue, bone and dentin

* Laparoscopes
* Arthoscopes
* Draining systems
* Dental cements
* Dental fillings
* Skin staples

### Circulating blood

Contacts circulating blood

* Intravascular catheters
* Temporary pacemakers electrodes
* Oxygenators
* Extracorporeal oxygenators
* Dialysers
* Dialysis tubing
* Haemoadsorbents and immunoadsorbants

## Implant devices

### Tissue/bone

Devices principally contacting bone, tissues and tissue fluids

* orthopaedic pins
* paltes
* replacement joints
* bone prosthesis
* bone cements
* intra-osseus devices
* pacemakers
* drug supply devices
* nerurmuscular sensors and stimulators
* replacement tendons
* breast implants
* artificial larynxes
* subperiosteal implants
* ligation clips
* intra-utrine devices

blood contacting devices

* pacemaker electrodes
* artificaial venous fistulae
* heart valves
* vascular grafts
* internal drug delivery catherters and ventricular assist devices

# Categorisation by duration of contact

Anticipated duration of contact

* Starting components
* Intermediate reaction products

## Limited exposure

Cumulative single, multiple or repeated use contact is upto 24h

## Prolonged exposure

Cumulative single, multiple repeated use contact is upto exceed 24 hrs but not 30 days

## Permanent contact

Single, multiple repeated use contact is greater than 30D

# Biological evaluation process

* Material characterisation
  + Pre clinical and clinical safety and totxicology data exists
  + Nature and duration of body contact
  + Constituent chemicals
  + Residual process aids
  + Additives used
* Established history of safe use in intended application
* Identity and quantity of novel materials and chemical present established and measured
* Known toxicological data, intended dose,rout,frequency, exposure adequate safety margins must be maintained
* Known leachable chemical mixtures, potential synergies of the leachable chemicals should be considered
* Entire amount of chemical were to leach out
  + Appropriate extraction testing
  + Simulating clinical exposure
* Potential for degradation
  + Manufacture
  + Sterilization
  + Transport
  + Storage
  + Use

# Biological evaluation test

## General

* Testing perfomed on final product, sterile
* Representative samples
* Materials processed in same manner
* Choice of test procedure
  + Nature
  + Degree
  + Duration
  + Frequency
  + Conditions of exposure
  + Contact of humans in normal intended use
  + Chemical nature
  + Physical nature
  + Toxicological activity
  + Systemic effects
  + Presence of leachable chemicals
  + Known and acceptable toxicity profiles
  + Device surface area to body size
  + Literature
  + Previous experience
  + Non-clinical tests
  + Sensitivity and specificity of test
  + Protection of human health
  + Protection of animal welfare

## Test descriptions:

* Based on duration of contact and the categorisation of human contact of the device the test applicability is specified in the matrix

### Cytotoxicity

* Cell culture technique- lysis of cell(cell death)
* Inhibition of cell growth
* Colony formation
* Other effects on the cell

### Delayed type hypersensitivity

Estimate potential for contact sensitization

Allergic or sensitization reactions

### Irritation

Including intracutaneous reactivity

Skin, eye, mucous mebrane, materials and their extracts

Test appropriate to route and duration of contact

Intracutaneous reactivity test to asses the localized reaction of tissue

Determination of irritation by dermal or mucosal test inappropriate for implants or blood contact

### Systemic toxicity(Acute)

* Potential absorption of toxic leachables and degradation products
* Estimate potential harmfull effects of either single or multiple exposures less than 24hrs
* Pyrogenicity test
  + Material mediated pyrogenicity reactions of extracts
  + Endotoxin contaminated
* Combined with subacute and subchronic toxicity and implantation protocols

### Sub acute and subchronic toxicity

* Effect of single or multiple exposure period of not less than 24hrs to a period not greater than 10% of total life-span of the test animal

### Genotoxicity

* Mammalian or non-mammalian cell culture
* Gene mutations
* Change in chromosomal structure

### Implantation

* Local pathological effects on living tissue
* Gross level
* Microscopic level
* Local and systemic effects
* Acute, subacute, shronic toxicity testing

### Haemocompatibility

* Haemolysis
* Degree of red cell lysis
* Release of haemoglobin
* Simulate geometry
* Contact conditions
* Flow dynamics

### Chronic toxicity

* Major period of the test animal- 6 mos

### Carcinogenicity

* Determine tumorogenic potential
* Lifetime studies
* Transgenic models

### Reproductive and developmental toxicity

* Effects on
  + Reproductive function
  + Embryonic development(teratogenicity)
  + Prenatal and early postnatal developmemt
* Bio-assays- for device having potential impact

### Biodegradation

* Biodegradable device
* Device use more than 30d
* Toxic release indication of device
* Parameters affecting rate of degradation described and documented
* Mechanism of degradation described
* Mechanism simulated in-vivo
* Rated of degradation determined
* Estimate exposure of degration and release of potentially toxic chemicals

### Toxicokinetic studies

* Evluate(ADME)
  + Absorptiton
  + Distribution
  + Metabolism
  + Excretion
* Determine delivered dose to the target organ
* Health hazard modelling using pharmacokinetic modelling(PBPK)
* Extrapolation of test report across gender,age,species and dose/exposure
* Potential and designed degradation products, leaachables, shall be taken into account
* Theoretical degradation processes investigated prior to study(in vitro- tissue, homogenates or cells)
* Must for bioresorbable
  + Permanent implsnt, corrosion is known or likely
  + Substantial quantities of potentially toxic or reactive degradation roducts likely to br released
* Release of leachables and degradation products are too lowfor metals, alloys, and ceramics to justify toxicokinetic studies.

### Immunotoxicology

* Chemical nature of the materials to potential immunotoxicological effects

# Interpretation of biological evaluation data and overall biological safety Assessment

* Strategy of programme
* Criteria to determining acceptability
* Risk management plan
* Adequacy of material characterisation
* Rationale for selecting and waiving of tests
* Additional data to complete biological evaluation
* Overall biological safety conclusions