

Regulatory Requirements for Medical Devices including In Vitro Diagnostics in India (Version 2.0)
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Lecture – L5
Regulatory Requirements of Biocompatibility of Medical Devices and ISO 10993

Welcome to Regulatory Requirements for Medical Devices including In Vitro Diagnostics in India version 2 lecture 5, lecture 5 that is Regulatory Requirement of the Biocompatibility of Medical Devices as per ISO 10993.

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The slide features the CDSA logo on the top left and the NPTEL logo on the top right. It contains three main sections: 'LEARNING OBJECTIVES' with the text 'Be aware of what is biological evaluation test of medical device (MD).', 'EXPECTED OUTCOME' with the text 'Able to understand: Requirements of biological evaluation of medical devices, Standards and regulatory guidance.', and 'TARGET AUDIENCE' with the text 'Personnel working in the medical device & IVD industries. Innovators or start ups involved in medical device or IVD industry, regulatory affairs personnel, human ethics committee members, clinical trial team members, researchers, academicians, students etc. and for persons generally interested in medical devices.' A video inset on the right shows Prof. Aseem Sahu at a podium. The footer of the slide reads 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

Learning objective this lecture, be aware what is the biological evaluation test? What is the requirement of these biological test of the medical devices? Expected outcome- the participants can able to understand, what is the requirement of the biological evaluation of the medical devices? What standards is applicable for the biological evaluation and the regulatory provisions for the requirement of biological evaluation test for medical devices?

Target audience, the personnell working in the medical devices and in vitro diagnostics industry, the startup involved in the medical devices and diagnostic industries, the regulatory affairs personnel, human ethics committee members, clinical trial team

member, researchers, students, academician and the person generally interested in the field of medical devices and in vitro diagnostics.

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The slide features a blue header with the title "WHAT WILL WE LEARN IN LECTURE 5?". Below the title, five white boxes with blue borders list the topics to be covered. The presenter, a man in a dark suit and glasses, stands to the right of the slide. The slide is framed by a blue border with a decorative bar at the bottom containing the text "REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)".

WHAT WILL WE LEARN IN LECTURE 5?

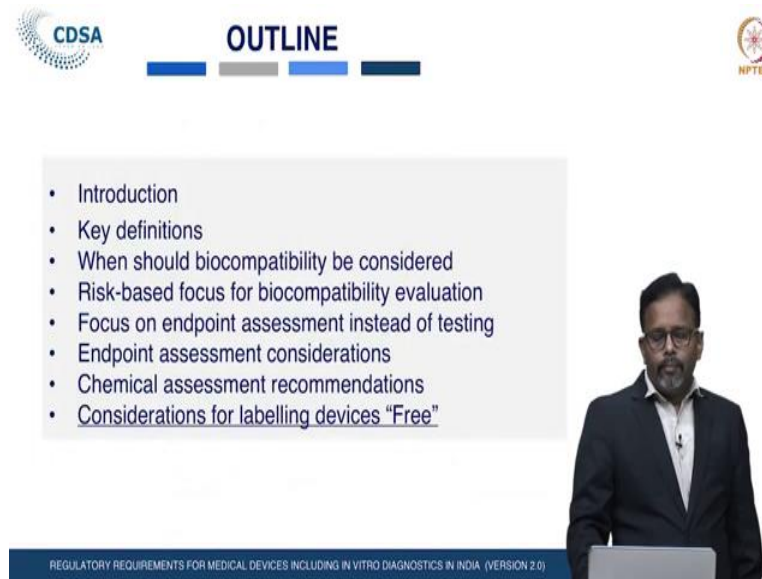
- What is a biocompatibility?
- Biological evaluation within risk management process
- Categorization of medical devices and test selection
- Standards for Biocompatibility Tests- ISO 10993
- General principles applying to biological evaluation of medical devices

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What will we learn in this lecture? First we will discuss what is the biocompatibility, then bio evaluation with risk management process what are the process for risk management process for biological evaluation, then categorization of the medical devices and test selection based on the category of the medical devices which type of biological evaluation is required.

The standards, the standards applicable for conducting the biological evaluation and the general principles of the standards prescribed for biological evaluation of the medical devices.

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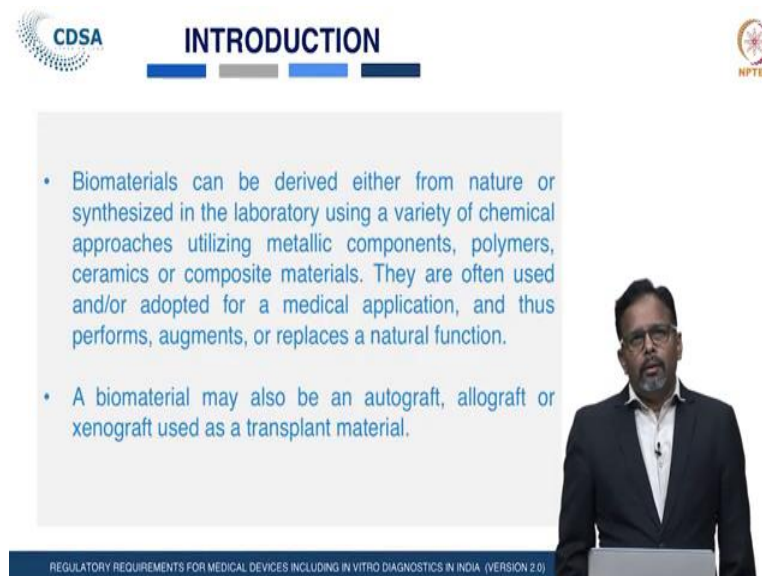


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- Introduction
- Key definitions
- When should biocompatibility be considered
- Risk-based focus for biocompatibility evaluation
- Focus on endpoint assessment instead of testing
- Endpoint assessment considerations
- Chemical assessment recommendations
- Considerations for labelling devices "Free"

So, all topics we will discuss in this lectures and we will have detailed discussions we will have the question answer session. Now, what is the bio materials?

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- Biomaterials can be derived either from nature or synthesized in the laboratory using a variety of chemical approaches utilizing metallic components, polymers, ceramics or composite materials. They are often used and/or adopted for a medical application, and thus performs, augments, or replaces a natural function.
- A biomaterial may also be an autograft, allograft or xenograft used as a transplant material.

Bio materials can be derived either from the nature or synthesized in the laboratory using the variety of the chemical process variety of the approach utilizing the metallic component, polymers, ceramics or composite materials. They are often used and adopted for a medical application and perform and replace the natural functions of the human body

This bio material may also be an autograft, allograft, xenograft used as a transplant material.

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- The purpose of performing biocompatibility testing is to determine the suitability of a device for human use, and to see whether use of the device can have any potentially harmful physiological effects.
- Material characterization and analysis of a device's components are conducted prior to any biological testing. This involves extracting leachable materials from the device or components at an elevated temperature, and analyzing the leachable extracts for potentially harmful chemicals or cytotoxicity.

In the bottom right corner, there is a small inset image of a man in a dark suit and glasses, presumably the presenter. At the bottom of the slide, there is a footer that reads: 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

The purpose of performing biocompatibility testing of these biomaterials is to determine whether the suitability of the devices for human use and to see whether use of the devices can have any potential harmful physiological effect on the human body. So, this is the purpose of the biocompatibility. The material characterization and analysis of the devices components are conducted prior to conduct of any biological evaluation, it is not that once the bio material is developed immediately the biological evaluation or biocompatibility test can be performed.

Prior to conduct of the biological evaluation the material characterizations and analysis of the devices is compulsory. This material characterization includes extracting leachable materials from the devices or the component at the elevated temperature and analyzing leachable extract for potential harmful chemicals or cytotoxicity.

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CDSA **INTRODUCTION** **NPTEL**

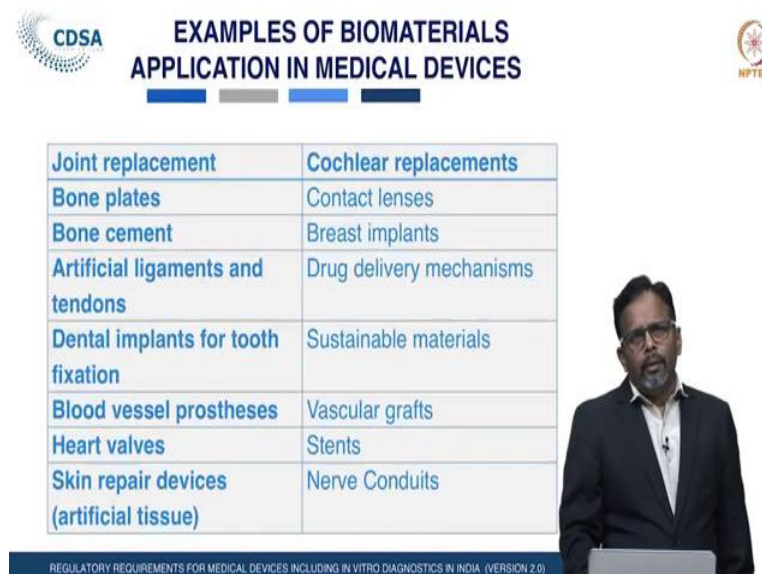
- Once in vitro testing has been completed, in vivo biological testing can be done based upon the device's intended use.
- This testing can range from skin irritation testing to hemocompatibility and implantation testing.
- Turnaround time for biocompatibility tests can range from three days to greater than several months, depending on the specific test data needed. Sub-chronic or chronic implantation testing can last even longer.
- The two ways to test the biocompatibility in vivo implant are "Tissue culture test" and "Blood and contact tests".

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Once this in vitro testing has completed the in-vivo biological test can be done based on the device intended use. The biological evaluation testing can be ranges from the skin irritation test to hemocompatibility test, implantation test etc.

The turnaround time for biocompatibility test can ranges from 3 days to greater than the several months, depending on the specific test data needed for the materials. The sub-chronic or chronic implantation test can last even longer period. The two ways to test the biocompatibility in vivo implants are "tissue culture test" and "blood and contact test".

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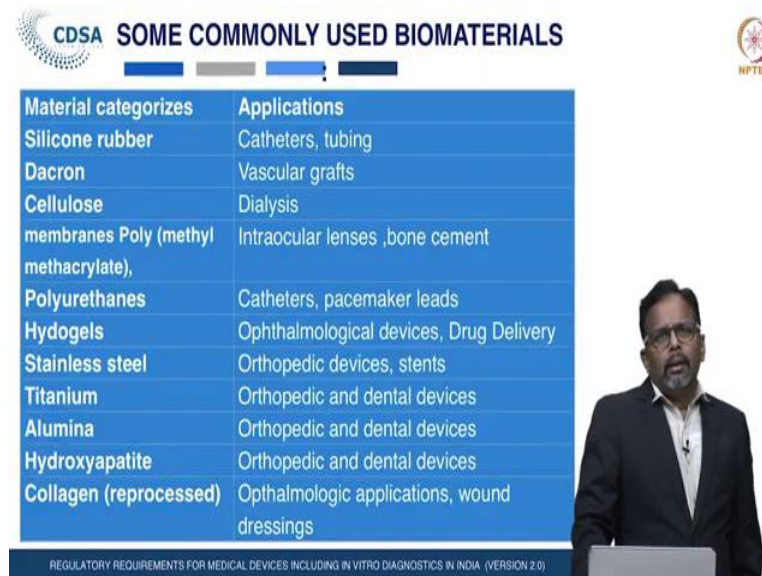
CDSA **EXAMPLES OF BIOMATERIALS APPLICATION IN MEDICAL DEVICES** **NPTEL**

Joint replacement	Cochlear replacements
Bone plates	Contact lenses
Bone cement	Breast implants
Artificial ligaments and tendons	Drug delivery mechanisms
Dental implants for tooth fixation	Sustainable materials
Blood vessel prostheses	Vascular grafts
Heart valves	Stents
Skin repair devices (artificial tissue)	Nerve Conduits

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The example we have discussed what is the biomaterials and the applications of the biomaterials. These biomaterials applications is meant for manufacturing of that joint replacement, bone plates, bone cements, artificial ligaments and tendons, heart valves, skin repair devices, breast implants, vascular grafts, stents, nerve conduits, contact lens these are the applications of the bio materials.

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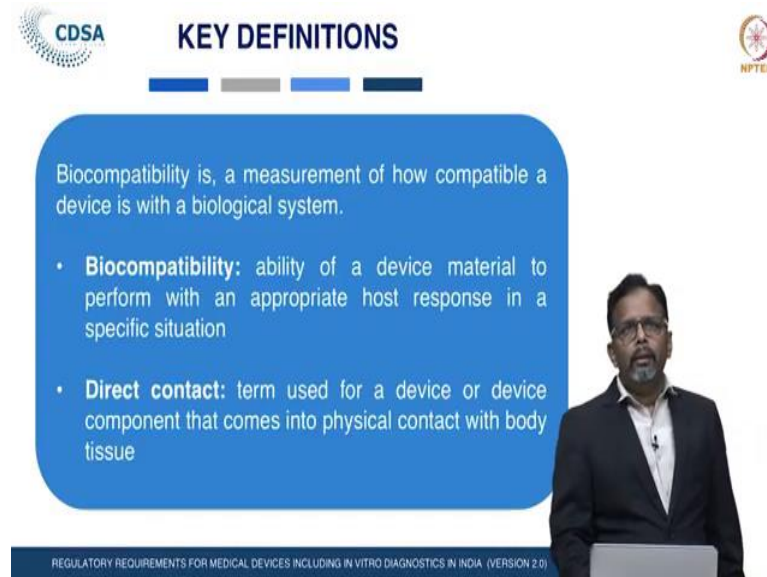
Material categorizes	Applications
Silicone rubber	Catheters, tubing
Dacron	Vascular grafts
Cellulose	Dialysis
membranes Poly (methyl methacrylate),	Intraocular lenses ,bone cement
Polyurethanes	Catheters, pacemaker leads
Hydrogels	Ophthalmological devices, Drug Delivery
Stainless steel	Orthopedic devices, stents
Titanium	Orthopedic and dental devices
Alumina	Orthopedic and dental devices
Hydroxyapatite	Orthopedic and dental devices
Collagen (reprocessed)	Ophthalmologic applications, wound dressings

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And which biomaterials are generally used for which applications we can discuss that, the various biomaterials are available like silicon rubbers. This material is to be generally used in the manufacturing of the catheters or tubes. Cellulose that is for the dialysis devices, polyurethanes that is used in the manufacturing of catheters, pacemaker leads. A stainless steel metals if you talk about the metals, the stainless steel that used in the orthopedic devices or cardiac stent, titanium that is also used in the orthopedic implants and also in the dental devices.

Alumina orthopedic and dental devices, hydroxyapatite that is also used in the orthopedic and dental implants, collagens ophthalmological applications or various wound dressing the collagens are to be used. So, these are the applications of the certain biomaterials which is used for applications of the manufacturing of these types of the medical devices. Now come to the definitions, certain definitions that related to the biocompatibility.

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CDSA **KEY DEFINITIONS** **NPTEL**

Biocompatibility is, a measurement of how compatible a device is with a biological system.

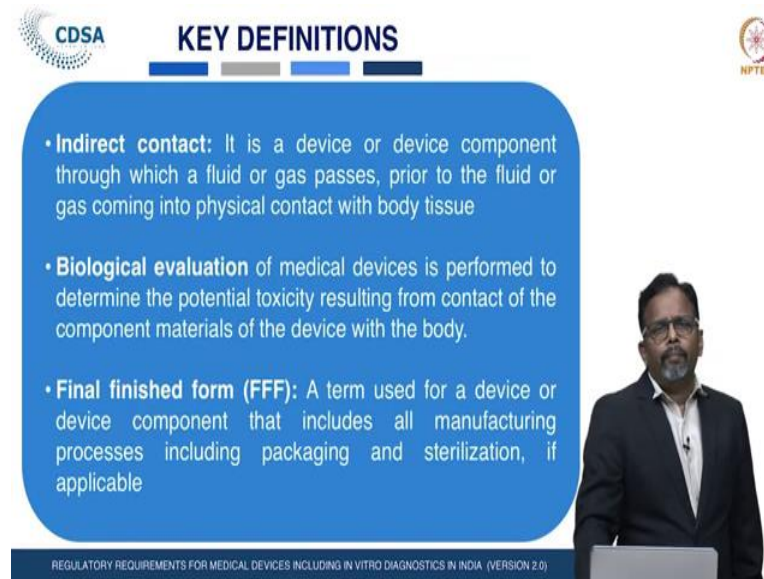
- **Biocompatibility:** ability of a device material to perform with an appropriate host response in a specific situation
- **Direct contact:** term used for a device or device component that comes into physical contact with body tissue

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First of all what is the biocompatibility? Biocompatibility is the measurement of how a compatible a device is with the biological system. Another way we can say it is the ability of the device material to perform with an appropriate host response in a specific situation.

Now, the other definition, that is direct contact or indirect contact, what is the indirect contact? Indirect contact is defined as the term that used for the devices or device component that comes into physical contact with the body tissue. If it is a physical contact with the body tissue it is considered as a direct contact.

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CDSA **KEY DEFINITIONS** **NPTEL**

- **Indirect contact:** It is a device or device component through which a fluid or gas passes, prior to the fluid or gas coming into physical contact with body tissue
- **Biological evaluation** of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body.
- **Final finished form (FFF):** A term used for a device or device component that includes all manufacturing processes including packaging and sterilization, if applicable

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What is indirect contact? The device or device component through which a fluid or gas passes prior to the fluid or gas coming into physical contact with the body or body tissue. So, it is such type of that devices or the device component through which a fluid or the gas passes prior to the fluid or gas coming into the physical contact with the body tissue that can be considered as indirect contact.

Now, biological evaluation it is also known as the biocompatibility the biological biological evaluation of the medical device is performed to determine the potential toxicity resulting from the contact of the component material of the device with the body, this is the biological evaluation. Now, finished form of the devices that is the final finished form this term used for the devices or device component that includes all manufacturing process including packaging crystallizations if applicable.

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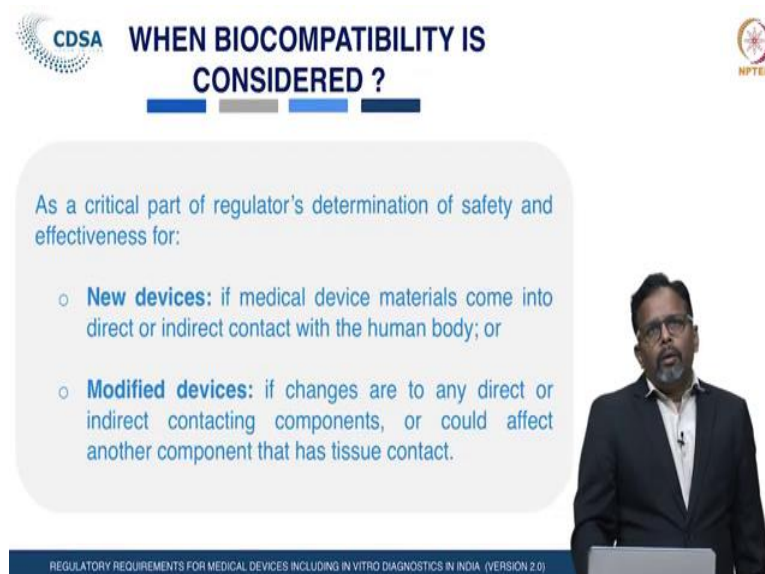
CDSA **KEY DEFINITIONS** **NPTEL**

- **Novel material:** material that has not previously been used in any medical device.
- **Sponsor:** manufacturer, submitter or applicant.

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Novel materials this term can be defined as the materials that has not previously being used in any medical devices new materials which is yet to be used in their particular applications. So, any new material that has not previously used in any medical devices is known as is termed as novel materials. A sponsor, means manufacturer, applications submitters, who will submit the application for regulatory approval or any purpose to the authorities that is done by a sponsor.

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CDSA **WHEN BIOCOMPATIBILITY IS CONSIDERED ?** **NPTEL**

As a critical part of regulator's determination of safety and effectiveness for:

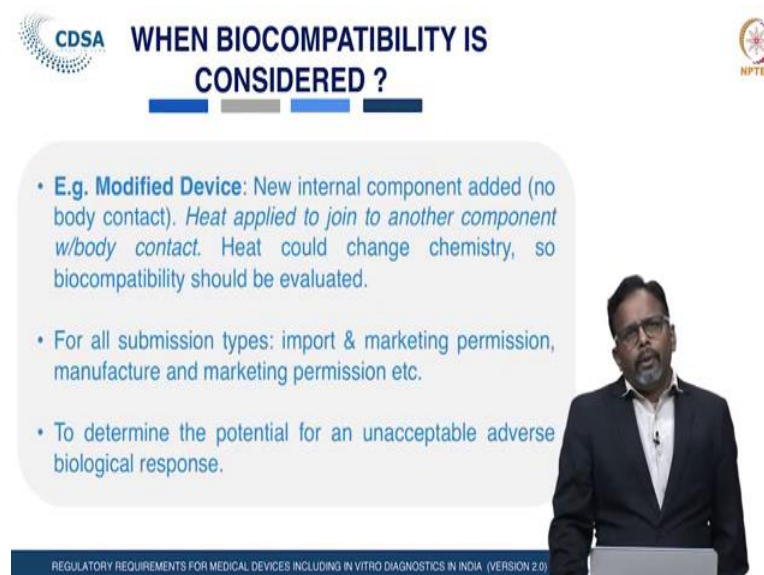
- **New devices:** if medical device materials come into direct or indirect contact with the human body; or
- **Modified devices:** if changes are to any direct or indirect contacting components, or could affect another component that has tissue contact.

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Now, come to the biocompatibility, given biocompatibility is considered we have to understand in which cases this biocompatibility test or the biological evaluation test can be considered. It is a critical part for the regulators determination of the safety and effectiveness of the new medical devices of the modified medical devices.

So, for any new devices if the medical devices, material come direct or indirect contact with the human body. Then the biological evaluation can be considered or if the particular changes have been made in the devices which affect another component which has come to the tissue contact in such cases this biological evaluation or bio compatibility test is also required.

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WHEN BIOCOMPATIBILITY IS CONSIDERED ?

- **E.g. Modified Device:** New internal component added (no body contact). Heat applied to join to another component w/body contact. Heat could change chemistry, so biocompatibility should be evaluated.
- For all submission types: import & marketing permission, manufacture and marketing permission etc.
- To determine the potential for an unacceptable adverse biological response.

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Modified devices why it is required, because in certain cases if the new internal component is added on the particular medical devices that added through some heat, heat is to be applied to join the another component with the main device. The heat could change the chemistry of the biomaterials so; in such cases the biocompatibility test is required.

This bio biological evaluation or the biocompatibility test is also required for submission of regulatory approval for import or the marketing permissions or manufacture and marketing permissions. Sometimes this study is required to determine the potential for unacceptable adverse biological response. So, in such cases this biological evaluation test can be performed on the medical devices or the component of the medical devices.

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The slide features the CDSA logo on the top left and the NPTEL logo on the top right. The main title is "WHEN BIOCOMPATIBILITY IS CONSIDERED ?". Below the title, a text box states: "Biocompatibility standards can be used to facilitate information submission to regulator:". This is followed by a bulleted list of standards: "ISO 10993-1 and related 10993 series of standards" and "ASTM, ICH, OECD and Pharmacopoeial biocompatibility standards". A presenter is visible on the right side of the slide. At the bottom, a footer reads: "REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)".

Now, the biocompatibility test It should be carried out as per applicable standards some biological evaluation test the standards have been prescribed in pharmacopoeia, some have been described certain guidelines or the standards have been describing other standards.

But the ISO 10993 that is the standards developed by ISO for biological evaluation of medical devices, various series of this standards are available and each series have different standards, guidance, principles that is included in the various series of the ISO 10993 also some ASTM or ICH or OECD guidelines are standards are also applicable and that is adopted by the other regulators.

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The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is "RISK BASED APPROACH (FOR BIOCOMPATIBILITY)". Below the title is a blue rounded rectangle containing the text "The ISO 10993-1, includes consideration of:" followed by a bulleted list. To the right of the slide is a man in a dark suit and glasses, standing behind a podium. At the bottom of the slide, there is a small text line: "REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA. (VERSION 2.0)".

**RISK BASED APPROACH
(FOR BIOCOMPATIBILITY)**

The ISO 10993-1, includes consideration of:

- device design, material components and manufacturing processes;
- clinical use of the device including the intended anatomical location;
- frequency and duration of exposure;
- potential risks from a biocompatibility perspective;

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We will discuss that the standards ISO 10993 which is applicable for determination of the biological evaluation of the medical devices as per our Medical Device Rule 2017. So, in India these standards it is in the law it is clearly defined that ISO 10993 where the biological evaluation has been prescribed that should be applicable for conduct of the conduct of this test.

So, what are the main component, principles, guidance and approach for conduct of the biological evaluation, we will have some brief discussion on this standards. What is the standards this ISO 10993, this standards include consideration of the design devices material component and manufacturing process. This also includes the clinical use of the medical devices including the intended anatomical locations where it is to be implanted or used.

The frequency and duration of the exposure, if the device if certain time it has to be exposed to the human body so, based on the frequency and duration of the devices the test can be decided. Potential risk from the biocompatibility perspective, if there any potential risk is there in such cases also this standards this includes the consideration of such cases also.

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CDSA RISK BASED APPROACH (FOR BIOCOMPATIBILITY)

- information available to address the identified risks; and
- information needed to address any remaining knowledge gaps, such as new biocompatibility testing or other evaluations that appropriately address the risks.

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If certain information is available to address the identify the risk any other risk and then information needed to address any remaining knowledge gaps certain gaps are there in particular materials such as the new biocompatibility testing or other evaluation that appropriately address the risks. In such cases what type of that evaluation is required to carry out on the biomaterials or the component of the medical devices or the medical devices all those parameters, that standards includes.

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The slide features the CDSA logo on the top left and the NPTEL logo on the top right. The title "RISK BASED APPROACH (FOR BIOCOMPATIBILITY)" is centered at the top. A blue rounded rectangle contains the text "New biocompatibility testing may not be needed if:" followed by two bullet points. A speaker in a dark suit and glasses stands on the right side of the slide, positioned behind a laptop. At the bottom, a dark blue bar contains the text "REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)".

CDSA RISK BASED APPROACH (FOR BIOCOMPATIBILITY)

New biocompatibility testing may not be needed if:

- The device is made of materials that: Have been well characterized chemically and physically in the published literature; and Have a long history of safe use;
- Materials and manufacturing information is provided to demonstrate that no new biocompatibility concerns exist.

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The biocompatibility test may not be needed, if the device is made of the material that has been well characterized chemically and the physically and also there is a lot of published literature is available and have long history of safe use, in such cases the bio evaluation test cannot be required or cannot be considered, provided the adequate literature and the data on the product or the biomaterial has to be produced by the manufacturers to justify whether this is required or not.

If the material or the manufacturing information is provided to demonstrate that no biocompatibility concerned is exist on the medical devices. So, in such cases it is not necessary to carry out the biological evaluation test.

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CDSA **RISK BASED APPROACH (FOR BIOCOMPATIBILITY)** **NPTEL**

It may be possible to leverage previously conducted biocompatibility information if:

- The previously tested device has similar indications, type, and duration of contact;
- An explicit statement is provided regarding any differences in materials or manufacturing between the new and leveraged devices under consideration; and
- Information is provided to explain why differences aren't expected to impact biocompatibility.

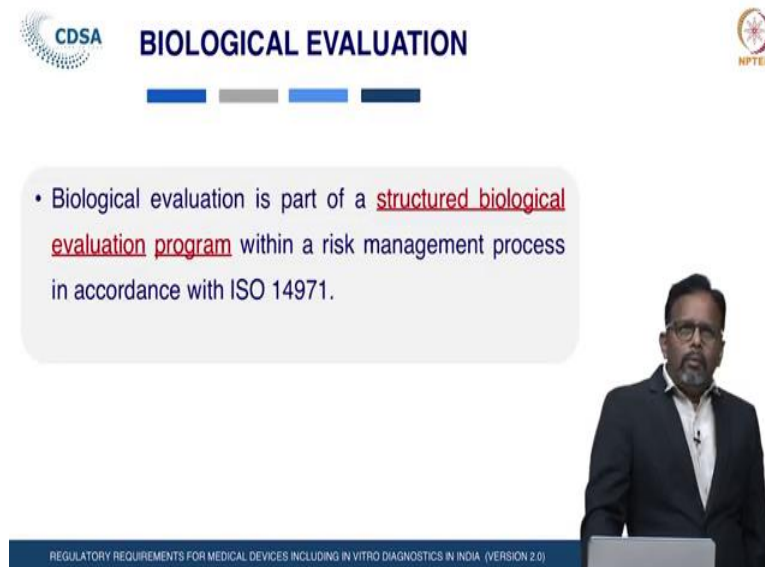
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If you see the risk based approach the bio evaluation biological evaluation may be possible to leverage the previously conducted biocompatibility formations. If the previously tested device have similar indication, similar type and also the duration of the contact of the device is the same, in such case also there is the compatibility study is not necessary.

The information provided by the manufacturer to explain why differences are not expected to impact the Biocompatibility. It meets the manufacturer has to justify properly adequately by way of the published literatures the study already performed earlier and the safe views history of the safe use of that devices. They can justify who are

not performing the biological evaluation with a particular medical devices or component of the medical devices.

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BIOLOGICAL EVALUATION

- Biological evaluation is part of a structured biological evaluation program within a risk management process in accordance with ISO 14971.

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Now, come to the biological evaluation, we have already discussed what is the biological evaluation, it is a part of a structure biological evaluation program within the risk management process in accordance with the ISO 14971 Risk Management Process(RMP) that ISO 14971 is applicable for all the medical devices and in vitro diagnostics. So, this biological evaluation study is the part of the risk management process in accordance with the 14971 ISO.

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CDSA **THE ISO 10993 SERIES** **NPTEL**

INTERNATIONAL STANDARD **ISO 10993-1**

Biological evaluation of medical devices —
Part 1: Evaluation and testing within a risk management process

- It a series of about 20 standards
- High level guidance on how to conduct a biological evaluation
- Detailed test methods for investigation of different aspects of biological safety
- Supporting guidance on materials characterization, use of reference materials, animal welfare, and more.
- Reference to other test methods and guidance in Pharmacopoeia and national standards.

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This ISO 10993 series we have discussed that it has various series and approximate 20 series of the standards is applicable 20 -22 standards are presently applicable for the biological evaluation. It is a high level guidance and how to conduct the biological evaluation, various types of the biological evaluation that procedure methods or guidance has been given in this standards. If you see the series 1, series 1 that is the general biological evaluation standards here are the details of the test method for the investigation of the disk different aspect of the biological safety.

That is given the annexures. it has 3 annexures and annexure A, annexure B and annexure C. Annexure A the matrix is available is given based on the categorization of the medical devices which test are required to conduct and which are not required that annexure A is there. Annexure B in which cases how to approach the risk based analysis of the devices and based on that what the study is required that manufacture can decide.

Annexure C that is the published literatures and the data review how to review that available data with respect to the biocompatibility of the particular biomaterials of the medical devices. So, this annexures provided in this ISO 10993 series we will discuss that.

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CDSA **THE ISO 10993-1** **NPTEL**

This part of ISO 10993 describes:

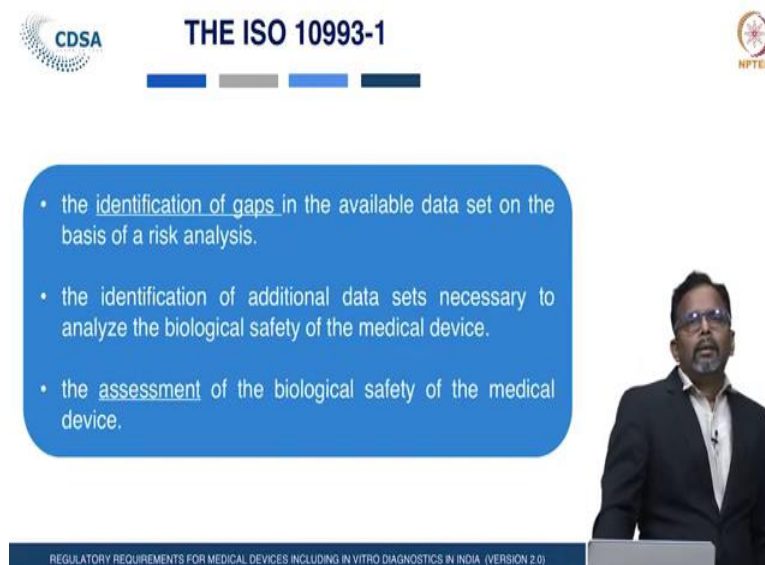
- the general principles governing the biological evaluation of medical devices within a risk management process.
- the general categorization of devices based on the nature and duration of their contact with the body.
- the evaluation of existing relevant data from all sources.

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We have discussed that the 10993 series 1 that is the general standards which describes the general principles of the biological evaluation. The categorization of the medical devices based on the nature and the duration of their contact with the body. this categorization is given in this ISO 10993 part 1.

The evaluation of the existing relevant data from all the sources, this describe the identification of the gap that based on the standards that based on the available information.

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CDSA **THE ISO 10993-1** **NPTEL**

- 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.

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The identification of gaps in the available data set on the basis of the risk analysis that can be carried out. The identification of the additional data set necessary to analyze the biological safety of the medical devices and the assessment of the biological safety of the medical devices. These component has been described in this first series of the standards annexure A already we have discussed .

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CDSA **THE ISO 10993-1** **NPTEL**

- Annex A contains an informative table that is generally helpful in identifying biological data sets recommended in the evaluation of medical devices, according to their category of body contact and duration of clinical exposure.
- Annex B contains guidance for the application of the risk management process. The biological evaluation shall be planned, carried out, and documented by knowledgeable and experienced professionals.

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Annexure A contains the informative tables it is applicable that in general helpful for identify the biological data sets recommended for evaluation of the medical devices; according to the category of the body and the duration of the exposure of the devices to the human body.


The appendix B that is the guidance for the application of the risk management process, how the risk management process is supplied the biological evolutions shall be planned, carried out and documented by the knowledgeable and experienced professionals.

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CDSA THE ISO 10993-1 NPTEL

- Annex C Suggested procedure for literature review, how to perform a literature review of existing data.

This part of ISO 10993 does not cover testing of materials and devices that do not come into direct or indirect contact with the patient's body, nor does it cover biological hazards arising from any mechanical failure.



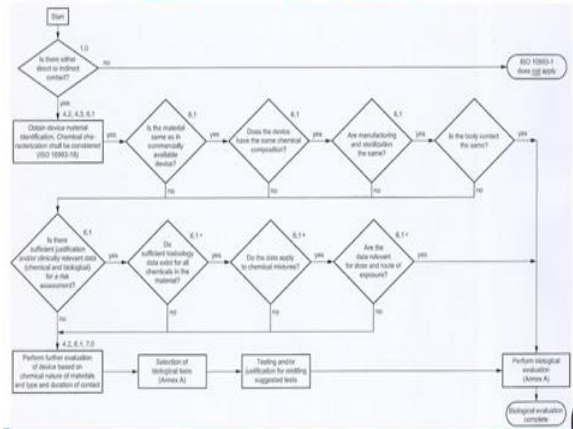
REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)

Annexure C that is the suggested procedure for the literature review, how to perform the literature review for the existing data, these are given in this annexure C of this standards. This ISO 10993 does not cover the testing of the materials or the devices which do not come into contact or indirect contact with the patient body, nor does it cover the biological hazards arising from any mechanical failure.


It means this standards, this biological evaluation test is only applicable to those devices which are direct or indirect contact with the patient body.

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CDSA SYSTEMATIC APPROACH TO A BIOLOGICAL EVALUATION OF MEDICAL DEVICES AS PART OF A RISK MANAGEMENT PROCESS NPTEL



REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)



Now, the risk approach to the biological evaluation of the medical devices as a risk management process we can discuss this, this flowchart you just see in this flowchart it is clearly mentioned that risk management process has been applied which cases this biological evaluation is required.

In which cases this it is not required and where the all the biological evaluation is required in which cases the it is not required and where the al the biological evaluation is required to be carried out this flowchart gives that detail idea. If you see the devices the manufacture can decide if the devices have direct or indirect contact with the human body or not.

If it is in direct contact or indirect contact with the human body then this standards is applicable and the biological evaluation can be carried out on such type of the devices. If it is not in direct contact or indirect contact with the human body the scope of this standard is not apply, that is in such type of devices this biological evaluation test is not required to be carried out.

If that biological evaluation that bio materials is direct or indirect contact with the human body, then the device identifications chemical and physical categorization of the devices shall be carried out by the manufacturers and also after carrying out the chemical categorization the requirement of the biological evaluation that can be decided.

We have discussed in the previous slides prior to conduct of the biological evaluation these chemical categorization of the medical devices or the biomaterials is required to be carried out to prove the safety, safety of the devices So, once it is conducted then the manufacturer has to see whether the biomaterials is the same which is commercially available in the market.

If it is commercially available then whether the devices have the same chemical component, if it is a same chemical component then also he has to see whether the manufacturing or the sterilization, the manufacturing of the devices the method applied for the manufacturing and the sterilization is the same which is already available medical devices.

If it is same then whether the body contact is also the same, if the commercially available device have the same sterilization process, same chemical composition, same body

contact in such cases the manufacturer has to perform the biological evaluation assessment as described in annex B of the standards.

They will carry out risk management process based on the data available and after that they have to decide whether which test is required and whether the test is carried out by the firm is sufficient to decide to whether the product is safe for use in the particular applications or the device is safe for use in the particular intended purpose.

If the manufacturing process commercially available devices, sterilization process or body contact is not the same as available in the market in such cases again they have to determine whether the sufficient data is available, sufficient justification is available, relevant data is there, the chemical and the biological detail of the medical devices or the bio material used in the medical devices is there.

If it is there that is sufficient for the risk assessment, if it is sufficient for the risk assessment then they have to see whether sufficient toxicology data exists for all the chemicals or the materials used in the biomaterials or the medical devices. If it is there then the data whatever the data that is applied to the chemical mixtures used in the biomaterials.

If the relevance data are there so, the does so, the data is also same to justify that it is based on this data the assessment can be determined and if all such data is available then they have to perform the biological risk assessment as per the annexure B of this standards. And, particular test based on the biological risk assessment the manufacture can perform and submit to the authority for the regulatory approvals or to establish the safety of the material or the medical devices being manufactured by the firm.

If there is no sufficient justifications or the relevant data of the chemical or the biological data of the medical devices is not available, then the manufacturer has to carry out the biological evaluation. They have to select the biological evaluation test as per the annexure A of these standards, annexure A which gives the details of the biological evaluation test carried out based on the categorization of the medical devices.

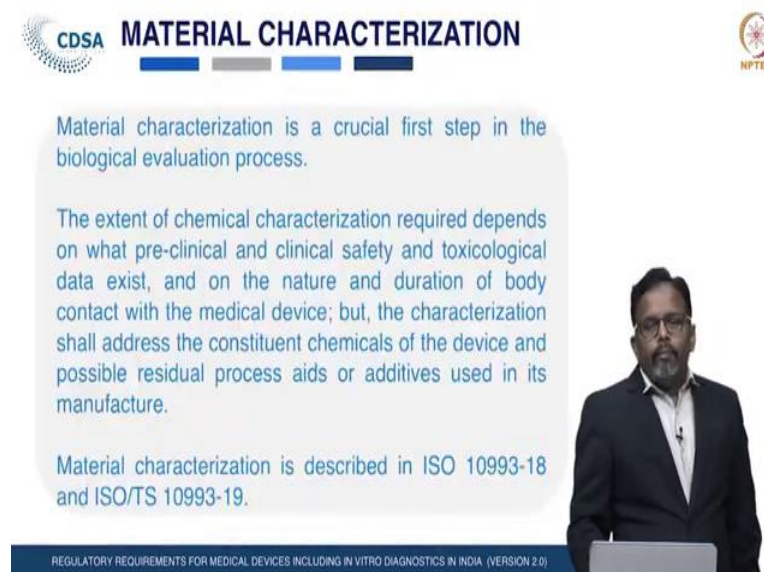
So, that matrix can be adopted by the manufacturers and based on that matrix the test prescribed in the annexures can be performed the ISO 10993 annexure A. That is the minimum test required to carry out the devices or the biomaterial for which there is a no

sufficient justifications or the relevant data with respect to the chemical or the biological information is available, but other test also can be carried out based on the nature of the devices.

So, that is the minimum test that has to be performed by the manufacturer in case there is a no adequate justification relevant data regarding the chemical or the biological is available with respect to the medical devices or biomaterials. And, after carrying out the biological evaluation as per the annexure A of the standards they have to justify in based on the data generated on the medical devices.

The product can be safe for use in the particular applications or used for the particular intended use of the devices and they have to submit the data to the authority for regulatory approvals or regulatory compliance.

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CDSA MATERIAL CHARACTERIZATION

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

The extent of chemical characterization required 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, the characterization shall address the constituent chemicals of the device and possible residual process aids or additives used in its manufacture.

Material characterization is described in ISO 10993-18 and ISO/TS 10993-19.

REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)

These are the principle or approach for conducting the biological evaluation and it is clearly mentioned in the standards, this is the standard that is 10993-1. And, this standards also recommended that the material characterization , material categorization are very important steps prior to conduct of the biological evaluation of the medical devices or the biomaterials.

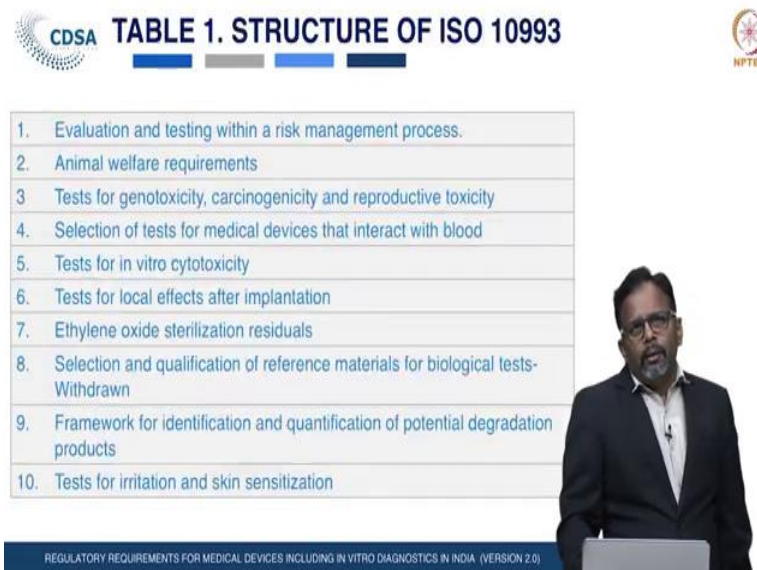
And, the material categorization is the is carried out that is based on the standards of the ISO 10993 that is series 18 and series 19 of the ISO standard 10993 describes the details

of the material characterization process methods. it is clearly mentioned in the this series 18 and 19 of the standards.

So, based on the that standards the material categorization is to be carried out to prior to conduct of the biological evaluation and based on this material categorization the data they can use for the for the biological evaluation test for the medical devices. The extent of the chemical categorization or the material categorization depends on what preclinical or the clinical safety and toxicological data exist on the devices or the materials.

The nature and duration of the body contact with the medical devices or the material but this categorization shall address the constituent chemicals of the devices and possible residual process aid or residual process aids or additives used in the manufacturing. And the details of the material categorization is prescribed in the series 18 or 18 and 19 of the ISO 10993.

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CDSA **TABLE 1. STRUCTURE OF ISO 10993** **NPTEL**

1.	Evaluation and testing within a risk management process.
2.	Animal welfare requirements
3.	Tests for genotoxicity, carcinogenicity and reproductive toxicity
4.	Selection of tests for medical devices that interact with blood
5.	Tests for in vitro cytotoxicity
6.	Tests for local effects after implantation
7.	Ethylene oxide sterilization residuals
8.	Selection and qualification of reference materials for biological tests- Withdrawn
9.	Framework for identification and quantification of potential degradation products
10.	Tests for irritation and skin sensitization

REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)

The various series of the biological evaluation is available so far published this there are approximate 22 standards series are there ISO 10993. The series 1 that we have discussed in detail that is for the evaluation in testing within the risk management process this is the general series. Series 2 of this standard that is, animal welfare requirement. Series 3 that is the, test for the genotoxicity causes genocity and productive toxicity. Series 4: that describes, the selection of the test of the medical devices that

interact with the blood. Series 5 describe the, test for the in vitro toxicity, how to conduct the in vitro cytotoxicity test, the methods have been described in this standards.

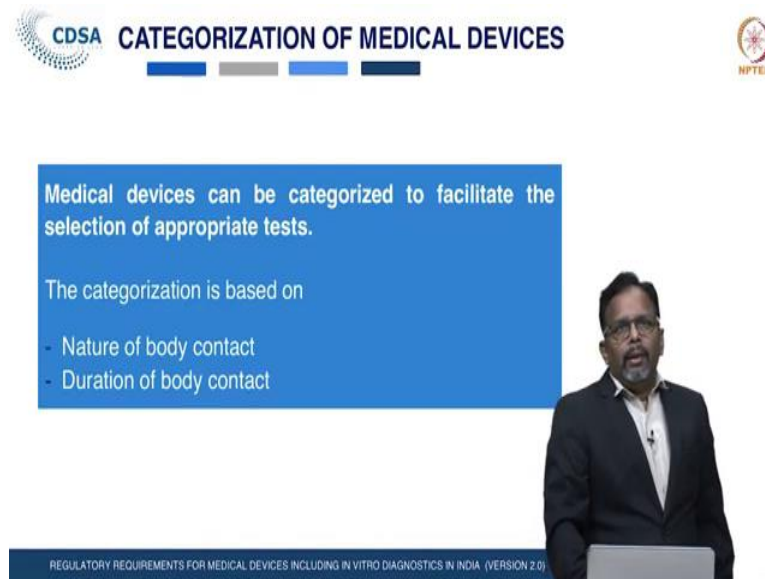
Series 6: that is the, test for local effects after implantation of the devices. Series 7 that is standards relates to the ethylene oxide sterilization residuals. Series 8 it is the selection and qualification of the reference materials for the biological test; however, the series has been withdrawn by the agency it is no more applicable. Series 9: that describe the framework for identification and quantification of the potential degradation products. Series 10 that describes the test for irritation or the skin sensitization test.

Series 11 of this standard that describe the test for the systematic toxic case study, series 12 describes the sample preparation and the reference materials, series 13 that is the identification and quantification of the degradation product from the polymeric medical devices. Series 14 that is identification quantification of degradation product from the ceramics, series 15 that is identification and quantification of the degradation product from the metal and alloy, series 16 that describe the toxico kinetic study design for degradation product and leachables.

Series 17 that is that describes the establishment of allowable limits for the leachable substance, series 18 chemical characterization of the materials we have discussed that this series 18 and 19 that describes the chemical categorization of the materials physicochemical, morphological or topographical categorization of the materials. Series 20: that is the principles and method for immunotoxicology testing of the medical devices.

These are the series of their standards which describes different that component in different test that is required to be carried out as a part of the biological evaluation of the medical devices. Now, we will discuss the categorization of the medical devices and the tessellation. We have discussed earlier that categorization of the medical devices as per the standard ISO 10993 that is based on the contact of the devices or the duration of the devices with the human body and based on this categorization which test is required to be carried out for biological evaluation of the biomaterial or bio compatibility that can be determined.

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The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is 'CATEGORIZATION OF MEDICAL DEVICES'. A blue text box contains the following text:

Medical devices can be categorized to facilitate the selection of appropriate tests.

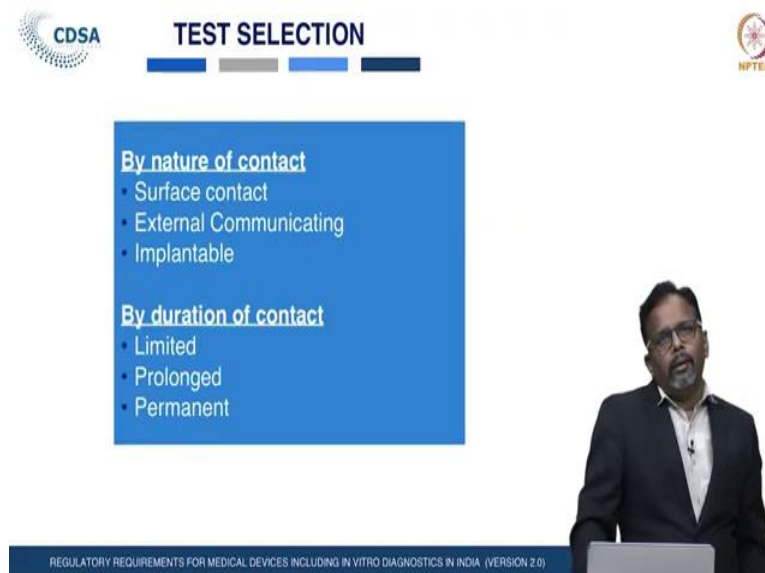
The categorization is based on

- Nature of body contact
- Duration of body contact

A speaker in a dark suit is visible on the right side of the slide. At the bottom, a footer reads 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

So, categorization of the medical devices already we have discussed that medical devices can be categorized to facilitate the selection of the appropriate biological test based on the nature of the body contact and duration of the body contact.

(Refer Slide Time: 43:06)



The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is 'TEST SELECTION'. A blue text box contains the following text:

By nature of contact

- Surface contact
- External Communicating
- Implantable

By duration of contact

- Limited
- Prolonged
- Permanent

A speaker in a dark suit is visible on the right side of the slide. At the bottom, a footer reads 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

If you see the nature of the body contact the nature of the body contact that device can contact with the surface of the body, certain devices that contact that external communicating devices and certain devices that is implantable devices. So, 3 different nature of the contact of the devices that is the surface contact, external communicating

and then implantable devices And, duration of the contact that is defined as a limited duration of the contact, prolonged duration of the contract or permanent duration of the contact.

So, limited contact, prolonged contact and permanent contact duration that is defined in terms of the duration then if it is in body contact up to 24 hours it can be consider as a limited contact, 24 hours to 30 days can be categorized as prolonged contact and the permanent beyond 30 days. If the, particular device is implanted or in contact with human body, that can be considered as a permanent contact devices.

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CDSA **SURFACE CONTACT DEVICE** **NPTEL**

- **Skin**
 - Devices that only contact intact skin surfaces.
 - Examples: Electrodes, tapes, compression bandages, various monitor probes, external orthopaedic braces.
- **Mucous membranes**
 - Devices that contact intact mucous membranes.
 - Examples: Feeding tubes, endoscopes, endotracheal tubes, oral swabs, intrauterine devices.

REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)

So, let us discuss the surface contact devices the devices which in contact with the skin that example of such type of devices are surgical tapes, bandages, probes, probes that is used in the certain devices, then external orthopedic braces. So, such type of devices can be which can be contact with this can is considered as a skin contact devices. Mucous membrane devices, the devices that contact intact with mucous membranes that is endoscopic, endotracheal tubes, oral swabs or the intrauterine devices.

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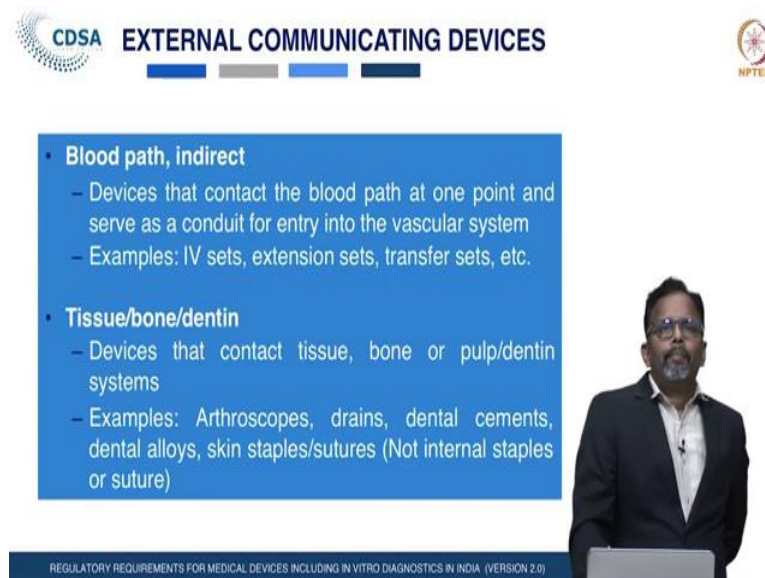


The slide features the CDSA logo on the left and the NPTEL logo on the right. The title 'SURFACE CONTACT DEVICE' is centered at the top. Below the title, a list of examples is provided in a light blue box. A presenter in a dark suit and glasses stands on the right side of the slide, positioned behind a laptop. At the bottom of the slide, a dark blue bar contains the text 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

- **Breached or compromised surfaces**
 - Devices that contact breached or otherwise compromised body surfaces
 - Examples: Dressings / bandages, for wounds, ulcers, burns...

Compromises surfaces or breached surfaces, the devices that contact, breaches or otherwise compromised body surfaces that dressings or the bandages for wounds or ulcers or the burns such devices which is in contact with such conditions that can be classified or considered as a breached or compromised surface contact devices.

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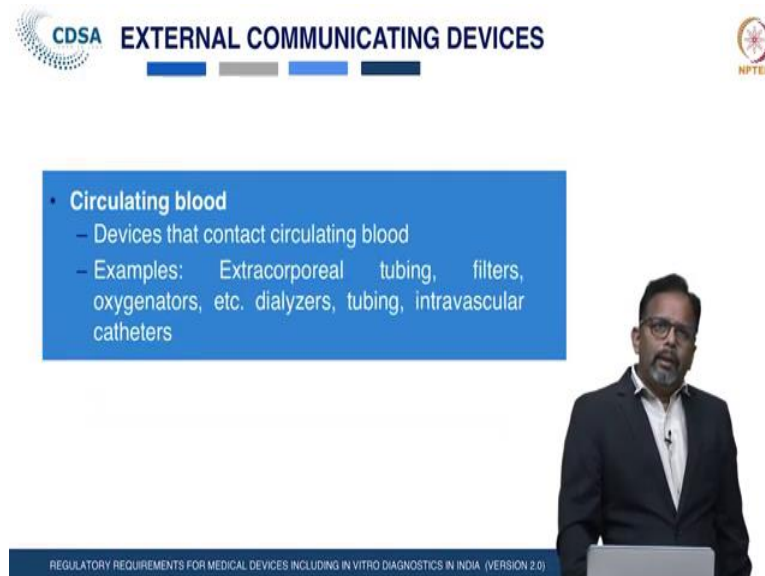
The slide features the CDSA logo on the left and the NPTEL logo on the right. The title 'EXTERNAL COMMUNICATING DEVICES' is centered at the top. Below the title, a list of examples is provided in a blue box. A presenter in a dark suit and glasses stands on the right side of the slide, positioned behind a laptop. At the bottom of the slide, a dark blue bar contains the text 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

- **Blood path, indirect**
 - Devices that contact the blood path at one point and serve as a conduit for entry into the vascular system
 - Examples: IV sets, extension sets, transfer sets, etc.
- **Tissue/bone/dentin**
 - Devices that contact tissue, bone or pulp/dentin systems
 - Examples: Arthroscopes, drains, dental cements, dental alloys, skin staples/sutures (Not internal staples or suture)

External communicating devices this also further divided into the nature of the contact if the devices that contact the blood path at one point and serve as the conduits for entry into the vascular system like intravascular sets, extension tubes, transfer sets, etc..

The devices that contact the tissue, bone or dentine systems that is considered as a tissue, bound dentine devices.

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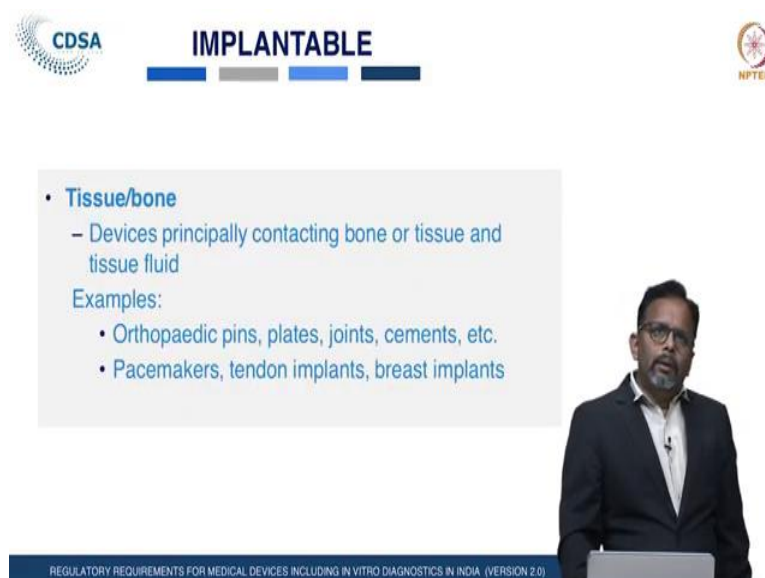
The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is "EXTERNAL COMMUNICATING DEVICES". A blue box contains the following text:

- **Circulating blood**
 - Devices that contact circulating blood
 - Examples: Extracorporeal tubing, filters, oxygenators, etc. dialyzers, tubing, intravascular catheters

A speaker in a dark suit is visible on the right side of the slide, standing behind a laptop. At the bottom, a dark blue bar contains the text "REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)".

Or the circulating blood devices that devices that contact the circulating bloods example of these devices are oxygenator and intravascular catheters, dialyzers.

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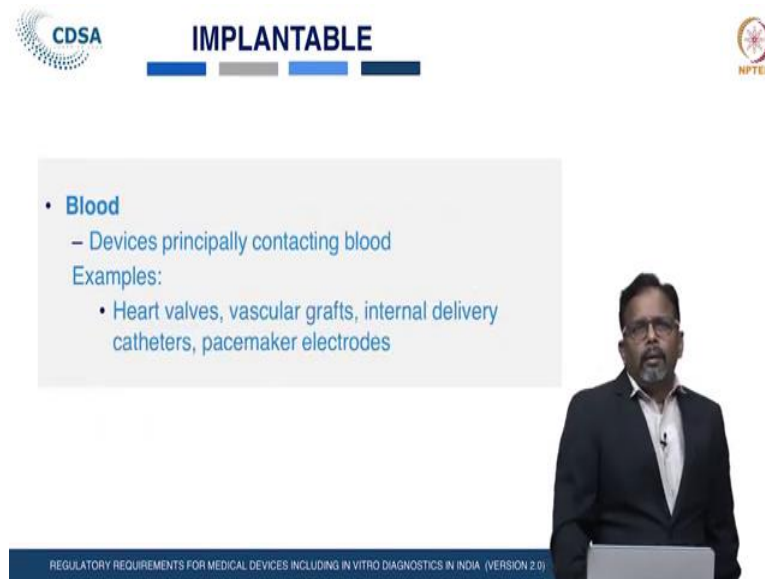
The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is "IMPLANTABLE". A light blue box contains the following text:

- **Tissue/bone**
 - Devices principally contacting bone or tissue and tissue fluidExamples:
 - Orthopaedic pins, plates, joints, cements, etc.
 - Pacemakers, tendon implants, breast implants

A speaker in a dark suit is visible on the right side of the slide, standing behind a laptop. At the bottom, a dark blue bar contains the text "REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)".

Implantable devices, the devices contacting the bone or the tissue and tissue fluids examples are the pacemakers, breast implants, orthopaedic implants.

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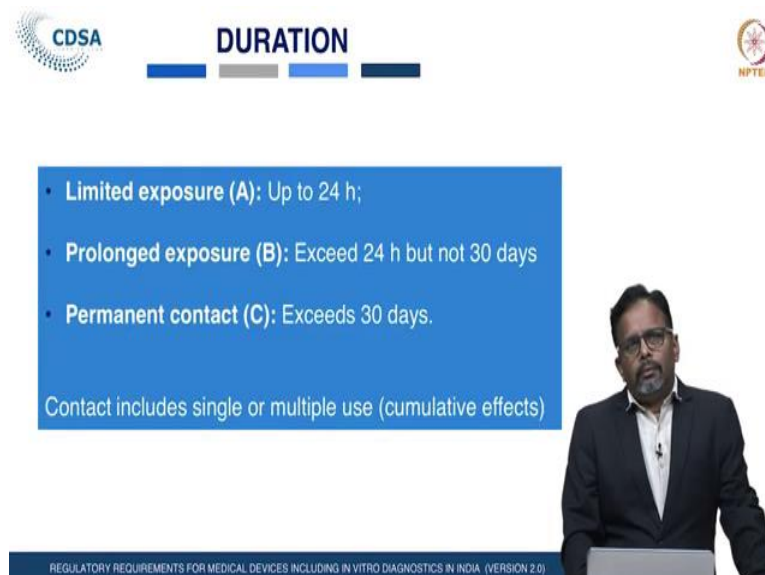
The slide features the CDSA logo on the left and the NPTEL logo on the right. The title 'IMPLANTABLE' is centered at the top. Below the title, a list of items is presented:

- **Blood**
 - Devices principally contacting blood
- Examples:
 - Heart valves, vascular grafts, internal delivery catheters, pacemaker electrodes

A presenter is visible in the bottom right corner of the slide frame. At the bottom of the slide, the text reads: 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'

The blood implantable devices, the devices principally contacting the bloods example of such type of devices are the heart valves is one of the example, vascular grafts, the pacemaker electrodes. So, these are the various types of the medical devices based on the types or the Category of the contact of the medical device with the human body.

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The slide features the CDSA logo on the left and the NPTEL logo on the right. The title 'DURATION' is centered at the top. Below the title, three categories of exposure are listed:

- **Limited exposure (A):** Up to 24 h;
- **Prolonged exposure (B):** Exceed 24 h but not 30 days
- **Permanent contact (C):** Exceeds 30 days.


Below the list, it states: 'Contact includes single or multiple use (cumulative effects)'. A presenter is visible in the bottom right corner of the slide frame. At the bottom of the slide, the text reads: 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'

That can be categorized into 3 main parts and the duration; duration of the contact that we have discussed, 3 types of the duration is prescribed in the standards. So, limited exposures that is the devices is in contact with the human body up to 24 hours Prolonged


exposure that is defined as the devices which in contact with the human body for 24 hours to 30 days. And, the permanent contact devices that can be categorized if the device is in contact with the human body which exceeded 30 days.

The contact includes the single or multiple uses the cumulative effect of the devices can also be considered as a based on the use of the devices that also be considered as a permanent contact devices, if it can be used multiple times beyond 30 days.

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BIOLOGICAL EVALUATION TESTS FOR CONSIDERATION ANNEX A



Category	Contact	Device Categorization		Biological Effect							
		Duration A - limited (<24h) B - prolonged (>24h, <30d) C - permanent (>30d)	Cytotoxicity	Sensitization	Irritation	Systemic Toxicity (acute)	Biocompatibility	Toxicity	Genotoxicity	Immunotoxicity	Hemocompatibility
Surface device	Mucosal Membrane	A	X	X	X						
		B	X	X	X						
		C	X	X	X						
	Bleached or compromised surface	A	X	X	X						
		B	X	X	X						
		C	X	X	X						
External communicating device	Blood Path, indirect	A	X	X	X						
		B	X	X	X						
		C	X	X	X						
	Tissue/bone/teeth	A	X	X	X						
		B	X	X	X						
		C	X	X	X						
Circulating blood	A	X	X	X							
	B	X	X	X							
	C	X	X	X							
Implant device	Tissue/bone	A	X	X	X						
		B	X	X	X						
	Blood	A	X	X	X						
		C	X	X	X						


For particular medical devices, different sets of tests may be necessary, including either more or less testing than is indicated in the Table. In addition to the framework set out in Table, the following should be considered based on a risk assessment, which considers the specific nature and duration of exposure: chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities.



REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)


This is the appendix A that is the matrix based on the device categorization, we have discussed that device categorization is based on the category of the devices with the contact of the human body and the duration of the contact. This table gives which mandatory tests are required for the medical devices where there is a no biological evaluation data or the toxicity data are available.

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ISO 10993 TEST MATRIX

ISO 10993-test matrix



DEVICE CATEGORIES		CONTACT DURATION			BIOLOGICAL EFFECT											
		A - Limited (≤ 14 hours)	B - Prolonged (14 hours - 30 days)	C - Permanent (> 30 days)	Cytotoxicity	Sensitization	Irritation or Intra-tissue Reactions	Systemic Toxicity	Material-Mediated Toxicity	Pyrogenicity	Sub-chronic Toxicity	Genotoxicity	Implantation by Hemocompatibility	Chronic Toxicity	Carcinogenicity	
BODY CONTACT	Intact skin	A	X	X	X											
	Mucosal membrane	A	X	X	X											
	Breached or compromised surface	A	X	X	X											
SURFACE DEVICES	Blood path, indirect	A	X	X	X											
	Tissue/bone	A	X	X	X											
	Circulating blood	A	X	X	X											
EXTERNALY COMMUNICATING DEVICES (Inhalers, catheters, diaphragms, dental filling materials, laparoscopes)	Intact skin	A	X	X	X											
	Mucosal membrane	A	X	X	X											
	Breached or compromised surface	A	X	X	X											
IMPLANT DEVICES	Tissue/bone	A	X	X	X											
	Circulating blood	A	X	X	X											
	Intact skin	A	X	X	X											


REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)

Notes:

- X Standard ISO evaluation tests
- O Additional tests which may be applicable
- Note 1: Tissue includes tissue fluid and subcutaneous spaces
- Note 2: For all devices used in extracorporeal circuits


The device is noble in nature or the biomaterial is used first time in such cases based on their category, the duration of the contact and the nature of the contact of the devices. These certain test that is prescribed in the standards, that is the cytotoxicity, sensitization test, irritation test, systematic toxicity test, subchronic toxicity studies, genotoxicity, implantation test, hemocompatibility test.

(Refer Slide Time: 50:24)



ISO 10993 TEST MATRIX

ISO 10993-test matrix



Medical device categorization by		CONTACT DURATION			BIOLOGICAL EFFECT											
		A - Limited (≤ 14 h)	B - prolonged (> 14 h to 30 d)	C - permanent (> 30 d)	Cytotoxicity	Sensitization	Irritation or Intra-tissue Reactions	Systemic Toxicity	Material-Mediated Toxicity	Pyrogenicity	Sub-chronic Toxicity	Genotoxicity	Implantation by Hemocompatibility	Chronic Toxicity	Carcinogenicity	
Category	Intact skin	A	X	X	X											
	Mucosal membrane	A	X	X	X											
	Breached or compromised surface	A	X	X	X											
Surface device	Blood path, indirect	A	X	X	X											
	Tissue/bone	A	X	X	X											
	Circulating blood	A	X	X	X											
EXTERNALY COMMUNICATING DEVICES	Intact skin	A	X	X	X											
	Mucosal membrane	A	X	X	X											
	Breached or compromised surface	A	X	X	X											
IMPLANT DEVICES	Tissue/bone	A	X	X	X											
	Circulating blood	A	X	X	X											
	Intact skin	A	X	X	X											

REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)

Notes:

- X ISO 10993:2009 recommended endpoints for consideration; O Additional FDA recommended endpoints for consideration

These are the minimum test that is required to be carried out by the manufacturers. If you see these standards ISO 10993 if you compare with the US guidelines in USA certain additional test is also required to be carried out.

And, this table shows which are the additional test is required to be carried out on the particular devices based on the categorization of the devices, certain additional test is performed, but this test is as per the requirement of US FDA and however, the manufacturer can do the test based on the available standards and they can justify after carrying out the risk base assessment of the particular medical devices.

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The slide features the CDSA logo on the left and the NPTEL logo on the right. The title is 'ENDPOINT ASSESSMENT VS. TESTING (CONT.)'. Below the title is a decorative bar with four colored segments: blue, grey, blue, and dark blue. The main content is a blue box with white text containing three bullet points. To the right of the blue box is a photograph of a man in a dark suit and glasses, standing behind a laptop. At the bottom of the slide, there is a dark blue footer with white text.

- Biocompatibility evaluation:
- All endpoints identified by an "X" or "O" in Annexure A may not be relevant for all devices in a particular category.
- For novel materials or manufacturing processes, additional evaluations beyond those recommended in Annexure A may be needed.

REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)

The end point identified by "X" or the "O" in annexure A may not be relevant for all the devices in particular category. We have discussed that it is only applicable for the devices where the there is no data is available with respect to the material chemical data or the biological evaluation data or the toxicity data in such cases these test can be, the test prescribing the annexure A can be carried out.

And this is the minimum test already I have explained that the additional test that as per the US FDA what are the additional test that is also mentioned in the another table which is given in the slides and although these test which is given in the table is not the complete test. It is the minimum test beyond those recommended that annexure A other test as appropriate that can also be performed by the manufacturers and also that can be

recommended by the regulators to perform that particular additional test which is not mention in the annexure A of the annexure A of this table.

(Refer Slide Time: 53:05)

The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is 'CATEGORIES OF BASIC EVALUATION TESTS'. Below the title is a list of eight evaluation tests for consideration:

1. Cytotoxicity
2. Sensitization
3. Irritation or Intracutaneous Reactivity
4. Systemic toxicity (acute)
5. Sub-acute and sub-chronic toxicity
6. Genotoxicity
7. Implantation
8. Haemocompatibility

A presenter is visible on the right side of the slide. At the bottom, there is a footer: 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

Now, the basic evaluation test we have discussed that is a cytotoxicity test, sensitization test, irritation or intracutaneous activity test, systemic toxicity, sub-acute or sub-chronic toxicity test, genotoxicity test, implantation test and haemocompatibility test.

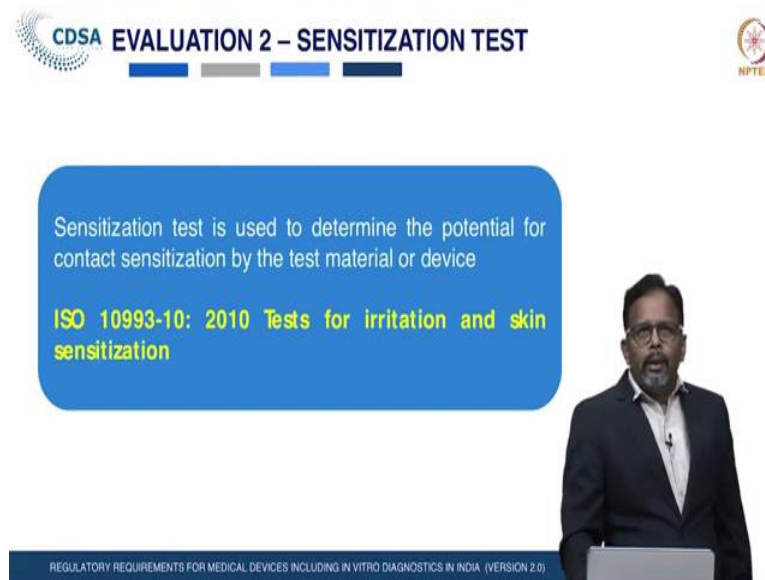
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The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is 'EVALUATION 1 - IN VITRO CYTOTOXICITY TEST'. The text describes the test: 'Using cell culture techniques, the test is used to determine the cell death, cell growth inhibition, and other adverse effects on cells caused by medical devices, materials and/or their extracts.' Below this, it states 'ISO 10993-5: 2009 Tests for *in vitro* cytotoxicity'. A presenter is visible on the right side of the slide. At the bottom, there is a footer: 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

The general purpose for conducting these test we can just have look the cytotoxicity test that is performed to determine the cell death or the cell growth inhibition. And, another

adverse event on the cells caused by the medical devices or materials or their extract and the details of the test to be performed by the manufacturers is given in the ISO 10993 series 5.

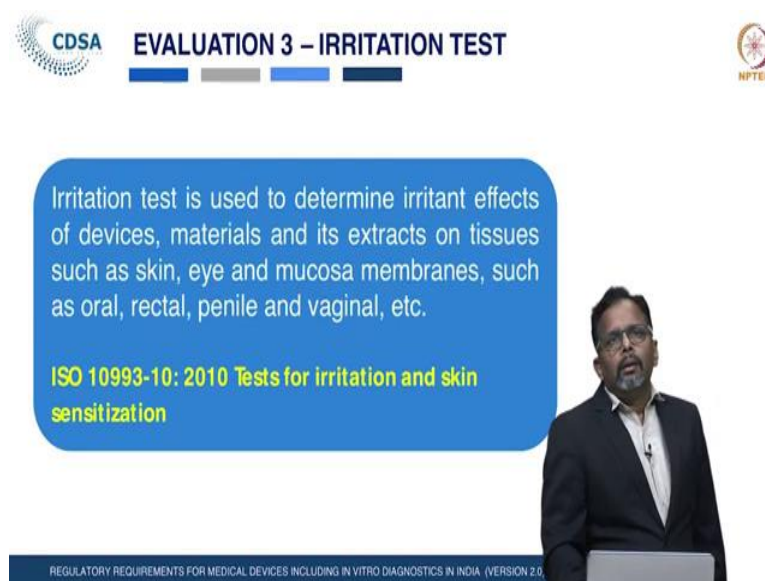
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The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is 'CDSA EVALUATION 2 – SENSITIZATION TEST'. A blue rounded rectangle contains the text: 'Sensitization test is used to determine the potential for contact sensitization by the test material or device' and 'ISO 10993-10: 2010 Tests for irritation and skin sensitization'. A speaker overlay of a man in a suit is positioned on the right side of the slide. At the bottom, a dark blue bar contains the text 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

Sensitization test, this test is to be used to determine the potential for contact sensitization by the test material or the devices the standards ISO 10993 series 10 which gives the details of the test which is to be performed.

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The slide features the CDSA logo on the left and the NPTEL logo on the right. The main title is 'CDSA EVALUATION 3 – IRRITATION TEST'. A blue rounded rectangle contains the text: 'Irritation test is used to determine irritant effects of devices, materials and its extracts on tissues such as skin, eye and mucosa membranes, such as oral, rectal, penile and vaginal, etc.' and 'ISO 10993-10: 2010 Tests for irritation and skin sensitization'. A speaker overlay of a man in a suit is positioned on the right side of the slide. At the bottom, a dark blue bar contains the text 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

Series 10 also includes the test for irritation this irritation test is used to determine the irritant effect of the medical devices or material or is extracted or the tissues such as the skin, eye or the mucous membrane.

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CDSA EVALUATION 4, 5 - SYSTEMIC TOXICITY TEST

Systemic toxicity	adverse effects
Acute □ 24 h	Shall carried out to determine the harmful effect of either single, multiple exposure or continuous exposures during the period of sample less than 24h
Subacute > 24 h and □ 28 d	occurring after multiple or continuous exposures between 24 h and 28 d "short-term repeated exposure systemic toxicity study" Subacute intravenous studies are generally defined as treatment durations of > 24h but < 14d.
Subchronic > 28 d and □ 90 d	occurring after the repeated or continuous administration of a test sample for a part of the lifespan (usually 90 d in rodents but not exceeding 10% of the lifespan of other species) Subchronic intravenous studies are generally defined as treatment durations of 14 d to 28 d.
Chronic usually 6 to 12 months	occurring after the repeated or continuous administration of a test sample for a major part of the lifespan

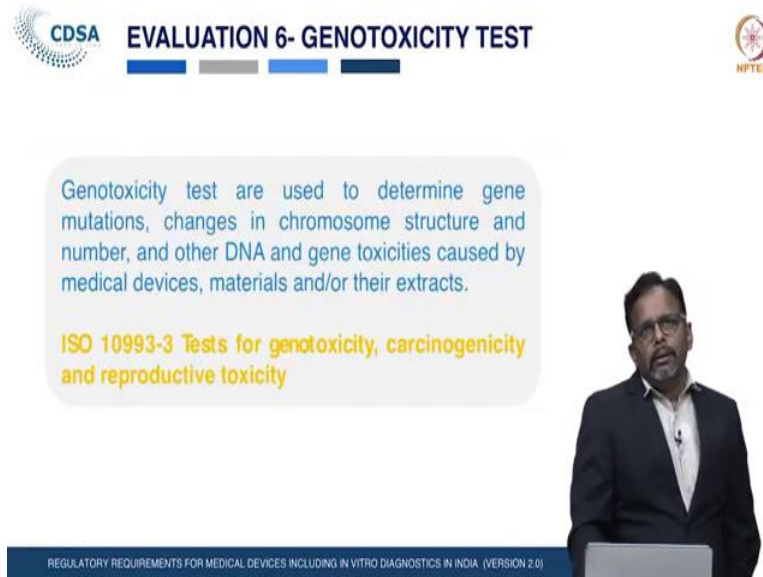
Systematic toxicity (Acute) Subacute and subchronic toxicity tests are given in ISO 10993-11.

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The main series 11 of ISO 10993 that describes the detail of the systematic toxicity study, under this study the acute toxicity study, sub acute toxicity study, subchronic and the chronic study that how to perform, how long that test can be performed that is given.

For acute toxicity that is to determine the harmful effect of the devices either by single or multiple exposure during the period of the sample, less than 24 hours. If the duration is between 24 to 28 days that sub acute toxicity is required to be carried out, if it is 28 days to 90 days then sub chronic and beyond 90 days that is chronic study is required to be carried and the duration of the chronic studies shall be carried out up to 6 month to 12 months and series 11 describes the details.

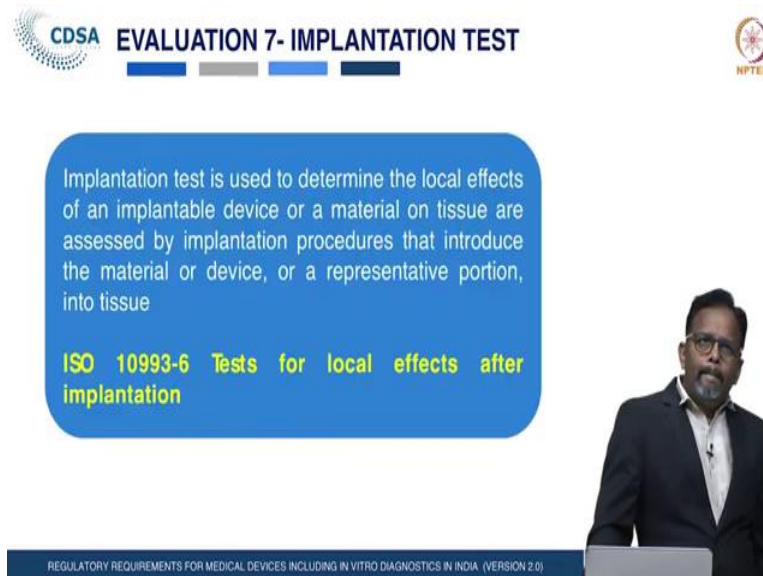
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The slide features the CDSA logo on the top left and the NPTEL logo on the top right. The main title is 'EVALUATION 6- GENOTOXICITY TEST'. A light blue rounded rectangle contains the text: 'Genotoxicity test are used to determine gene mutations, changes in chromosome structure and number, and other DNA and gene toxicities caused by medical devices, materials and/or their extracts.' Below this, in yellow text, it says 'ISO 10993-3 Tests for genotoxicity, carcinogenicity and reproductive toxicity'. On the right side, a man in a dark suit and glasses is speaking. At the bottom, a dark blue bar contains the text 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

Genotoxicity test: ISO 10993 series 3 that gives the details about the genotoxicity test, this test are used to determine the gene mutations, changes in the chromosome structures and the number and other DNA and gene toxicity caused by the medical devices or materials and or their extracts.

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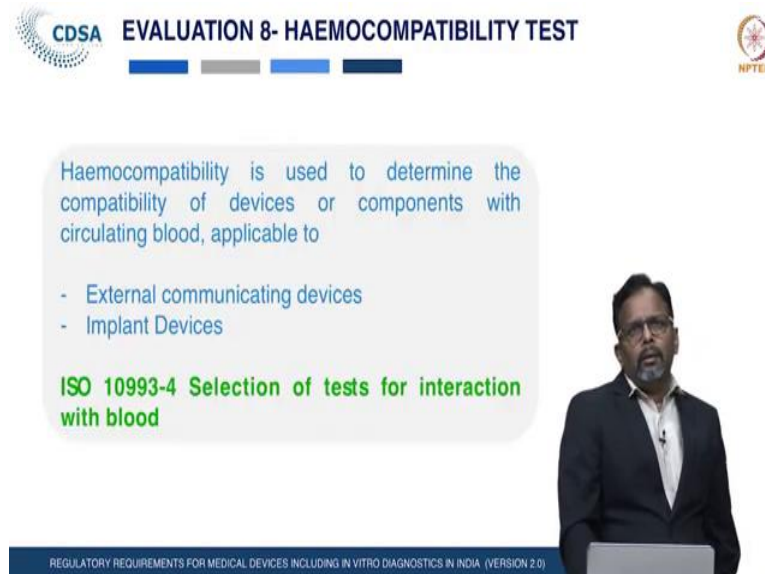


The slide features the CDSA logo on the top left and the NPTEL logo on the top right. The main title is 'EVALUATION 7- IMPLANTATION TEST'. A blue rounded rectangle contains the text: 'Implantation test is used to determine the local effects of an implantable device or a material on tissue are assessed by implantation procedures that introduce the material or device, or a representative portion, into tissue'. Below this, in yellow text, it says 'ISO 10993-6 Tests for local effects after implantation'. On the right side, a man in a dark suit and glasses is speaking. At the bottom, a dark blue bar contains the text 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

Implantation test: This test is used to determine the local effect of an implantable device or the material or the tissue by implantation procedure that introduced the material or the

devices into the tissue of the animals and series 10993-6 that gives the details of the implantation test.

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CDSA EVALUATION 8- HAEMOCOMPATIBILITY TEST

Haemocompatibility is used to determine the compatibility of devices or components with circulating blood, applicable to

- External communicating devices
- Implant Devices

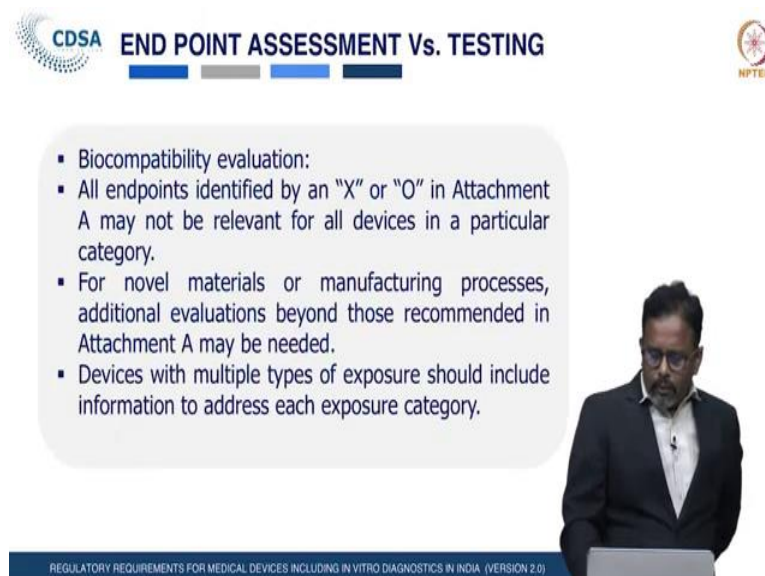
ISO 10993-4 Selection of tests for interaction with blood

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The slide features a speaker on the right side, a CDSA logo on the top left, and an NPTEL logo on the top right. The main content is enclosed in a light blue rounded rectangle.

Hemocompatibility test that is required to use the to determine the compatibility of the devices or the component with the circulating blood. And the series 10993 series 4 that gives the details of the haemocompatibility test study.

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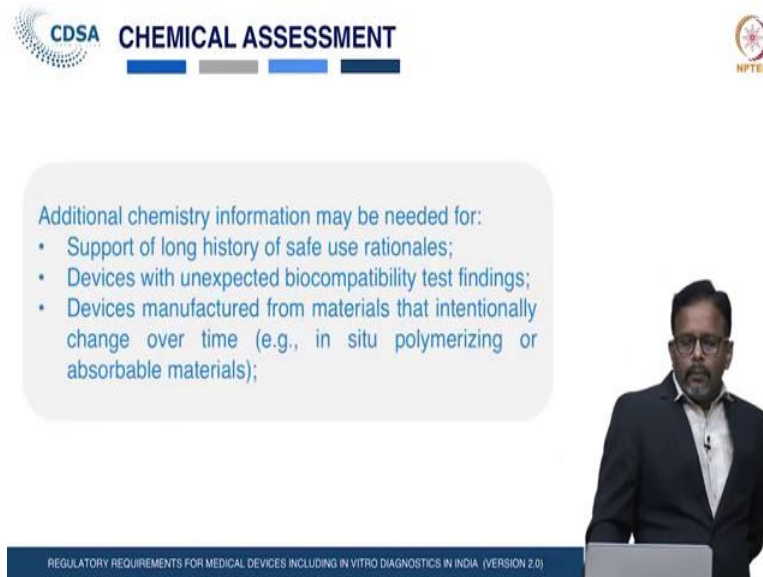
CDSA END POINT ASSESSMENT Vs. TESTING

- Biocompatibility evaluation:
- All endpoints identified by an "X" or "O" in Attachment A may not be relevant for all devices in a particular category.
- For novel materials or manufacturing processes, additional evaluations beyond those recommended in Attachment A may be needed.
- Devices with multiple types of exposure should include information to address each exposure category.

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The slide features a speaker on the right side, a CDSA logo on the top left, and an NPTEL logo on the top right. The main content is enclosed in a light blue rounded rectangle.

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CDSA CHEMICAL ASSESSMENT

Additional chemistry information may be needed for:

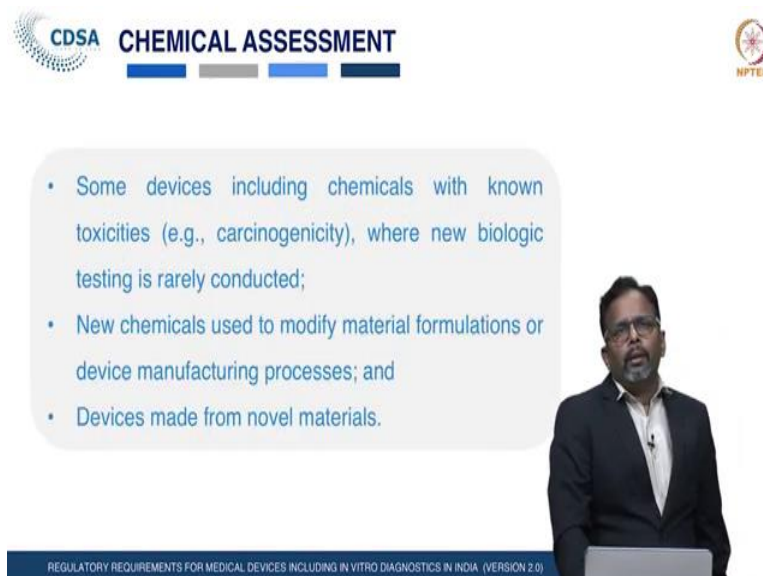
- Support of long history of safe use rationales;
- Devices with unexpected biocompatibility test findings;
- Devices manufactured from materials that intentionally change over time (e.g., in situ polymerizing or absorbable materials);

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Chemical assessment of the devices, we have already discussed that additional chemistry information also required to be carried out by the manufacturer to support the long history of the safe and use the rationales. These chemical assessment is also needed the devices with unexpected biocompatibility test findings. The device manufacturer from the material that intentionally change over a time, in such cases these chemical assessment is also required to be carried out by auto initiate the biological evaluation study.


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CDSA CHEMICAL ASSESSMENT

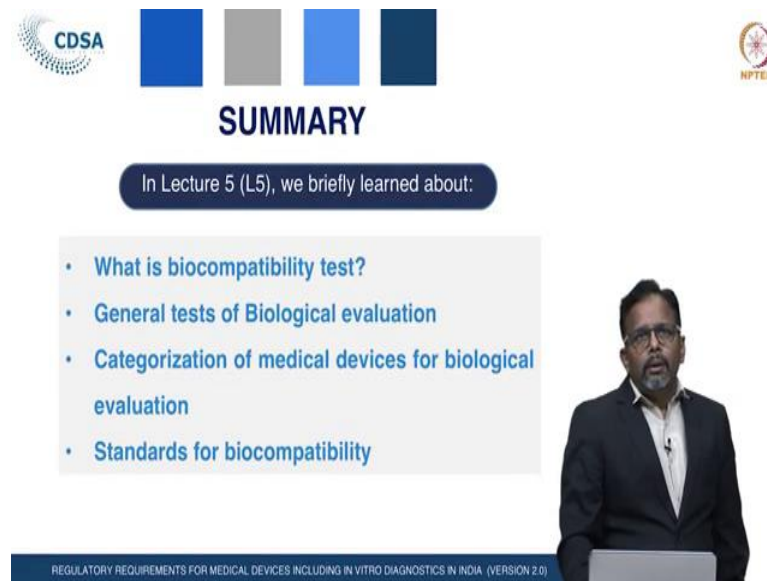
- Some devices including chemicals with known toxicities (e.g., carcinogenicity), where new biologic testing is rarely conducted;
- New chemicals used to modify material formulations or device manufacturing processes; and
- Devices made from novel materials.

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Some devices including the chemical with the known toxicity, where the new biologics testing is really conducted in such cases this chemical assessment is mandatory. New chemical entity used first time or modified material that formulation in such cases or the novel materials if it is used, then chemical assessment is mandatory prior to conduct the biological evaluation test of the medical devices or the material.

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The slide features the CDSA logo on the left and the NPTEL logo on the right. Below the logos is a decorative bar with four colored squares (blue, grey, light blue, dark blue). The word 'SUMMARY' is centered below the bar. A dark blue rounded rectangle contains the text 'In Lecture 5 (L5), we briefly learned about:'. Below this is a light grey box with a bulleted list of four items. To the right of the list is a video inset of a man in a suit. At the bottom, a dark blue footer contains the text 'REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)'.

- What is biocompatibility test?
- General tests of Biological evaluation
- Categorization of medical devices for biological evaluation
- Standards for biocompatibility

So, friends this is all about the biological evaluation, I hope you have now got the general idea about the biological evaluation test or biocompatibility test, what are the standards applicable for this, what are the guidelines, what is the risk based approach for selection of the biological evaluation test, categorization of the medical devices for the biological evaluation, how to categorize and the standards the main standards which is applicable for conducting the biological evaluation.

So, this is all about this lectures and before concluding this lectures let us have some question answer session question.

(Refer Slide Time: 59:23)

The slide is titled "RECAP" and features three numbered questions and their corresponding answers. The questions are:

1. Can you tell us what is the available Standards for biological evaluation of medical device?
Answer: ISO 10993
2. Fill in the blanks., There are about _____ series of ISO 10993.
Answer: Twenty
3. State true or false. Biological evaluation test does not apply for the device which is not in contact to human body.
Answer: True

The slide also includes the CDSA logo on the top left, the NPTEL logo on the top right, and a presenter standing on the right side. At the bottom, there is a footer that reads "REGULATORY REQUIREMENTS FOR MEDICAL DEVICES INCLUDING IN VITRO DIAGNOSTICS IN INDIA (VERSION 2.0)".

Now, the first question can you explain what is the applicable standards for conducting the biological evaluation of the medical devices as per Medical Device Rule 2017? Yeah, in the correct answer that we have long discussion on the standard that is ISO 10993. Now another that question key that, how many series of the ISO 10993 is there? Approximate we have discussed.

Student: (Refer Time: 60:01)

That more than 20 standards 20 series of the standards is available which covers the biological evaluation. Now, the last question, whether the biological evaluation test that is not under the purview of this ISO standards which type of the devices that cannot be in which the biological evaluation test is not applicable.

Yes devices which is not in contact to the human body in such type of the devices this biological evaluation test is not required that is ISO 10993 is not applicable for such type of devices. So, this is all about this biological evaluation test. Thank you very much and another topic we will discuss in subsequent lectures.

Thank you very much.