Regulatory Requirements for Medical Devices including In Vitro Diagnostics in India (Version 2.0)

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Lecture – L5
Standards of Medical Device, Quality Assurance and Testing

Dear friends again welcome to Regulatory Requirement for Medical Devices and In Vitro Diagnostic in India, lecture 5. Lecture 5 that is this Standards of the Medical Devices, Quality Assurance and Testing; this lecture will be given by Mr. Malay Mitra, Deputy Drugs Controller former having lot of experience and knowledge about the medical device regulation and vitro diagnostics.

So, in this lecture you will understand what is this standard; as you know that is standard is a document that provide the requirements, specifications, guidelines or definition of characteristic that can be used consistently to ensure that material products, process, services are fit for their purpose. So, this is the general definition of the standards. What types of the standard as specification; in this standards you will understand, in the medical devices this standards can be stabilized a wide range of this specification for the product, process and services.

These standards are essentially divided into horizontally standards and vertically standards. What will consider as a horizontally standard for the medical devices? Horizontally standards are those standards that apply equally to all medical devices; for example, if you see ISO 9001 or 9002 that is the standards for the Quality Management System (QMS) that is required for the manufacturing of the medical devices. Similarly, ISO 10993, that is this standards for the bio compatibility; that is standard is apply equally to all the medical devices.

Also ISO 11135 that is the sterilization; if manufacturer has to establish the different sterilization process, they have to confirm these standards, the part of the standards. Other horizontal standard you can say, ISO 15223 that is for symbols; symbols to be used in the label of the medical devices. So, these type of a standards is called as the horizontally standards. If you see the vertically standards; vertically standards that is applied to the specific products or the products groups.

If the product standard, you are talking about the product standard; ISO 4074 that is the product standards for natural rubber latex male condom. So, all the product standards all the condom shall confirm these standards that is called the vertically standards for the particular products. Also like ISO 10555 that is the standards for IV catheters. So, these product standards will be considered as a vertically standards for medical devices.

So, this type of the clarity or the standards you will discuss in the lectures is to be given by Mr. Malay Mitra. And, also recoganization of the standards; the standards is there, but if it is not recognized by the regulatory authority of the country of origin or the particular country, there is a no mandatory requirement of the standards. To have the mandatory requirement, the regulatory authority has to notify, has to certify these standards.

And, in the Medical Device Rule 2017 the rule 7 of the chapter 2; where the provision for establishment of the standards, product standards of the medical devices and in vitro diagnostics have been made. Under this rule the Central Assessing Authority (CLA), the Ministry of Health and Family Welfare (MoHFW) has made provision that the medical devices shall confirm the standards laid by the Bureau of Indian Standards. Bureau of Indian Standard (BIS); that is the standard setting organization in India, established in India.

And, the standards available for the medical devices and that devices are if regulated; then the BIS standard is applicable for the particular medical devices that is the vertical standards. Where there is a no relevant standards in the BIS or the standards approved by the licensing authority, Central Licensing Authority (CLA); then other internationally standards will be applicable. If other international standard is also not applicable; in that case the standards of the manufactures, validated standards of the manufacturers approved by the Central Licensing Authority (CLA) will be consider as a standard of the particular medical devices.

So, that provision have been made in the Medical Device Rule 2017 for reorganization of standards of the medical devices and the quality assurance also the testing methodology in the development and release of the medical devices, you will understand in the detail lecture.. So, be concentrate on the lectures; whatever the doubts questions you have, you can ask the experts and will further clarify the doubts. Thank you very much.

Welcome back again. Today our topic is Standards of Medical Devices, Quality Assurance and Testing. This is one of the series of lectures on medical devices and today's lecture is one of the most important lectures which will guide you to go through the standard medical device testing, how they are done, what are the parameters we followed and the this will give be a very very comprehensive idea about testing a medical devices.

Now, this presentation will, it is a overview basically. So, if you want to go through the further details, you have to pick up the topic and go into it later on.

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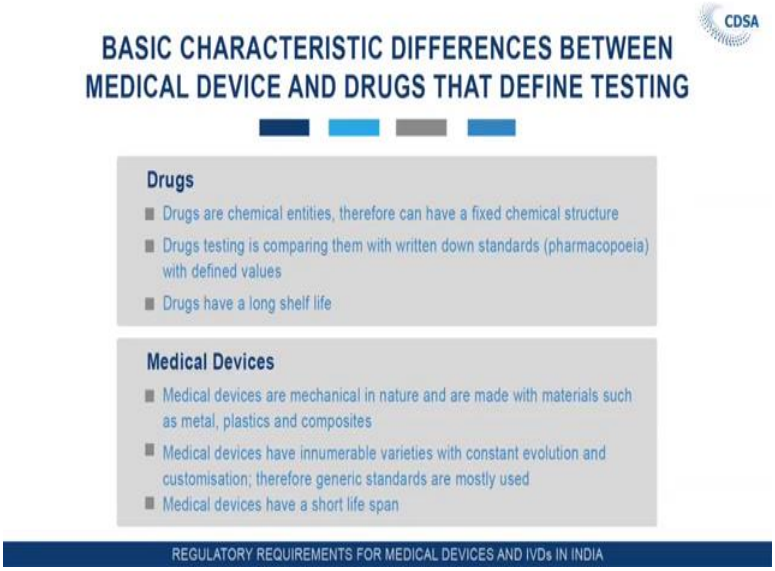

As usual before we start this presentation, I would like to give you a basic characteristic difference between medical device and drugs that define testing. Testing is very easy to understand testing in case of normal items; but in medical device it is something different. The basic differences between drug and medical devices is drugs are chemical entities, therefore, can have a fixed chemical structure.

Drug testing is compare a comparing them with written down standards pharmacopoeia with define values, and drugs have a long very long shelf life. This is what basically in three lines what drugs are. In case of medical devices; medical devices are mechanical in nature and are made with materials such as metals, plastics and composites. Medical devices have innumerable varieties with constant, evolution and customization; therefore, generic standards are mostly used. Medical devices have a short life span.

Now we understand that medical devices can be made of either plastic or metal or composites or anything else which are novel. So, in case of medical devices, testing standards cannot be a constant; they have to evolve with a product.

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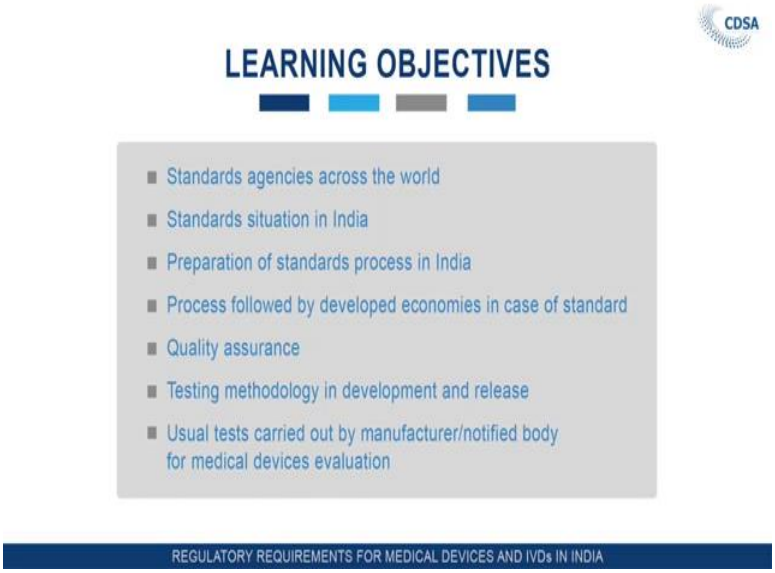

Purpose of this presentation; standard we will describe the standard agencies across the world, standard situation in India, preparation of standard process in India, process followed by developed economies in case of standard, quality assurance, testing methodology in development and release, usual test carried out by manufacturer notified body for medical device evaluation. This is basic structure of the presentation and each will be dealt with separately.

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Now, before we go further, let us know what are standards? The term formal standard refers specifically to a specification that has been approved by a standard testing organization that is a formal standard. You can of the informal standard of a product; but in case it is a formal standard, it has been approved by this standard sitting organization. What is a standard setting organization? It can it is in case of India, it is BIS. The term de jure standard refers to a standard mandated by legal requirements or refers generally to any formal standard. CDSCO standards accepted for notified medical devices. In cross, the terms de facto standard refers to a specification or protocol or technology that has achieved widespread use and acceptance, often without being approved by any standards organization or receiving such approval only after it has already has achieved widespread use.

Now, what does it mean? De facto standard is a standard which is in widespread use and has been accepted by the regulators and the government. So, that is a de facto standard.

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Example of de facto standards that are not approved by any standards organization or at least not approved until they were in widespread de facto use include the Hayes command set developed by Hayes, Apple's True type font design and the PCL protocol used by Hewlett Packard in the computer printed printers they produced.

These are standards which are de facto and have been accepted all around the world. Even in case of say, I will give a example of a de facto standard in case of say mobile devices; you have called this mobile mini USB chargers that standard was developed and is now widespread use in all the mobile phones.

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In case of medical device standard there are two organizations that typically issue internal standards I am talking about international standard there two organization; one is your International Organization Standardization that is ISO, we know ISO very well through the ISO 9001 which prevalent all over the world and organization for standards ISO and the International Electro Technical Commission IEC.

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I the ITU is a treaty based organization established as a permanent agency of the United Nations, in which governments are primarily members, although other organizations

such as nongovernmental organization and individual companies can also hold a form of direct membership status in the ITU as well. These standards are international standards, meaning they apply to the world. Consequently, even any given region or country could adopt them, perhaps with modifications or limitations. As in the case of BIS standards, we can adopt them straight away or we can modify them according to our rules and regulations and usage.

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Let us talk a bit about ISO, it is a non-governmental organization that develops and publishes international standards on a wide range of subject including medical equipment. This is this may be new to some of you that, ISO is a non-governmental organization; it is not control by any government. For the consumer, ISO standards ensure the products and services are safe, reliable and good quality.

For business, they are strategic tools that reduce costs by minimizing waste and errors and increasing productivity. These standards are very relevant for medical devices and incompose virtually every aspect of device design and implementation; for device inspection requirement, to guidelines for medical device labels.

For examples: ISO 13485 establishes a requirement for a Quality Management System for both the design and manufacturer of medical devices, which by the way has been accepted by the Indian medical device regulation 2017 as a quality management system. ISO 14179, it covers aspects including risk management, design control during product

development and verification and validation system. So, 14179 is also a standard, which if you follow that you will be eliminated risk in the production and design of the product

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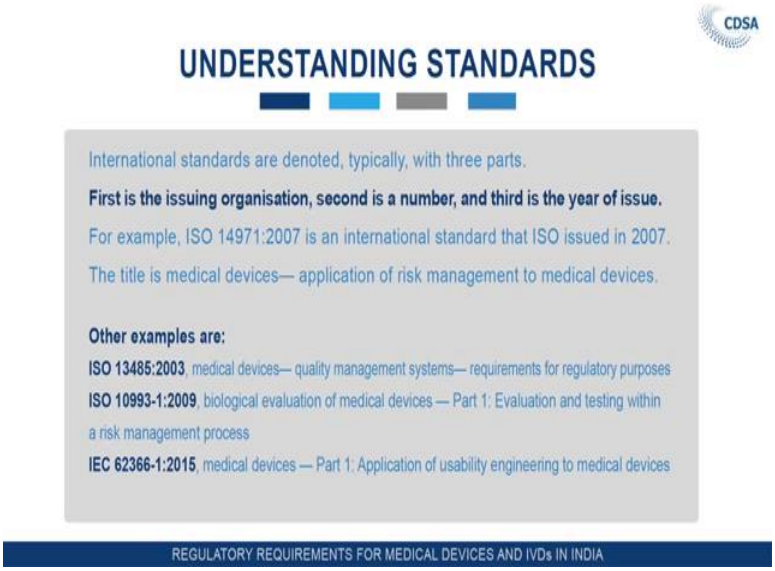

Understanding standards, you have seen international standards how they are labeled and named. International standards are denoted typically with three parts; the first is the issuing organization, second a number, and third is the year of issue. For example ISO 14971 .2007 is international standard that is issued in 2007. The title is medical device, application of risk management and medical devices.

Other examples are; ISO 13485. 2003 medical devices, quality management system, requirement for regulatory purposes which was issued in 2003. Similarly we have got the other two over there. So, once you get a standard, the number and the name you know who has issued it, what is the number of that standard and the year in which it was issued. So, in case there are two standards of the same name ISO 13485, you have to decide which year it was issued and the latest one denoting the last 4 digits, you have to use that for your as a standard.

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ISO will issue technical reports related to specific standard considered guidance documents that help the reader implement the standard. For our primary example, ISO has issued ISO TR 14969 2004, medical device, quality management system, guidance on the application of 13485. So, this standard ISO TR 14969 2004 is a standard again, which explain how to apply 13485 in your plan.

So, nothing is left to chance anywhere. In case ISO standard needs a correction, but is not significance enough to warrant creation of a new series, version of standard, corrigendum is published. For example, ISO 13485 2003 through technical corrigendum 1, published in 2009 to correct some typographical errors.

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Adoption, now we come to Bureau of Indian Standards BIS. As a standards organization, may adopt the international standard and in some cases they modify it or place a limitation on it. CDSCO Ministry of Health, Atomic Energy Regulatory Board, DOT as regulatory authority of the country may recognize the standard published by BIS and communicated it as mandatory standard, but there is no obligation to do so.

Practices in other countries; in USA you have the American National Standard Institute (ANSI); in the US representative to is it is the US representative to ISO. So, ISO is represented by in US USA is represented by ANSI in the ISO organization. ANSI is also composed of other US organization, that may become involved in adopting American National Standards. Two important organizations is in the area are the Association Advancement of Medical Instrumentation (AAMI) and the American Society for Quality (ASQ).

So, standards organization like ISO is actually taken care of by the members who were actually standard organizations of various countries. BIS is also a member of ISO from the Indian side.

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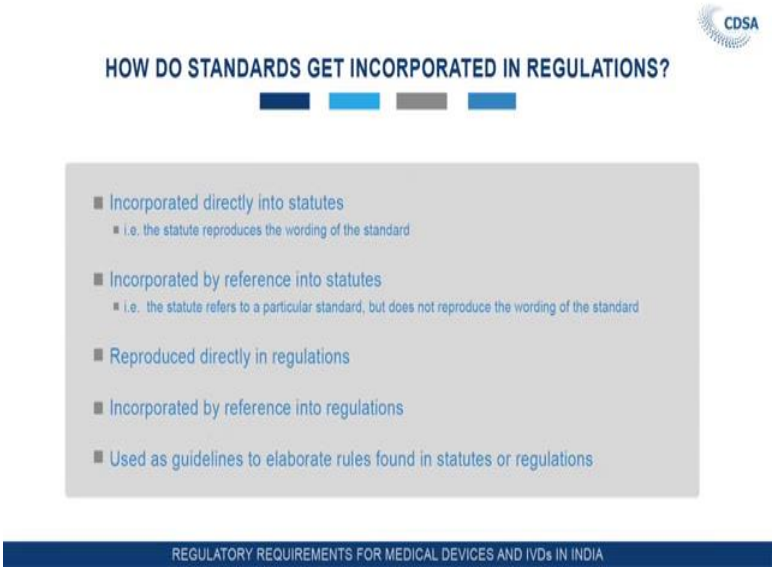

How do the standards get incorporated in? They can be incorporated to the regulations by various means. This is a simple slide to tell you, how they incorporated. This is not very important, because as far as we are concerned medical device whatever is written in ISO in medical device regulation 2017 actually takes care of that.

But still for a knowledge sake, let us know what how does it incorporated into regulations; it is either directly taken into a the statutes that is the statute reproduce the wording of the standards straight away, or it is referred to in the statutes for instance the schedule are refers to the ISO standards for syringes. It is reproduced directly in the regulations, incorporated by reference into regulations, used as guidelines to elaborate the rules found in statutes or regulations. These are the five different ways in which the international standards can find their way into rules.

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Product standards for medical devices particularly by rules by 2017; rule 7 of the regulations say, medical device shall confirm to the standard laid down by the BIS established on the section 3 of the BIS Act 1985 63 of 1985 or as be notified by the Ministry of Health and Family Welfare in the Central Government from time to time. So, BIS is the standards authority in case of medical devices. So, all standards of medical devices have to be complied to BIS standards as per the rule 7.

Where no relevant standard of medical devices has been laid down under Sub rule 1, such device shall confirm to the standard laid down by the International Organization for Standardization (ISO) or International Electro Technical Commission (IEC) or any other pharmacopoeial standards.

So, in case there is no BIS, relevant BIS standard available in the country; the manufacturer can take refuge in any other ISO standard in the world, or any other standard which is adopted by any other country officially. In case the standards which have not been specified under Sub rule 1 and Sub rule 2; the device shall conform to the validated manufactures standards. So, in case there is no standard available anywhere either in BIS or internationally, the manufacturer has to make his own standards and follow it.

This third question, third Sub rule 3 is the most important and quite relevant in case of standards of medical devices moving in the market or you intend to manufacturer

standards are which are not available any of the world. You have to develop your own standards and how to develop them, we will come to subsequent slides.

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Examples of BIS standards in Indian regulation where they find mention. Here I have given you two examples; one is QMS fundamentals and vocabulary, the standard developer is BIS, code is quality management and quality assurance, minister responsible is Ministry of Health, regulation is the Medical Device Regulations 2017, enabling statute Drug and Cosmetics Act 1940 and rule 1945. Remember, act actually enables the rules to take it. Location within the regulation; section 1, the definitions in this section apply to these regulations and then you have got links.

The second one is title of standard is risk management, standard develop by Bureau of Indian Standards (BIS), code is other standards regulated to quality, ministry responsible Ministry of Health, regulation medical devices regulations, enabling statute is again D and C act, location within legislation section 1 and then you have got links. You can go to the links and get the much more details about it.

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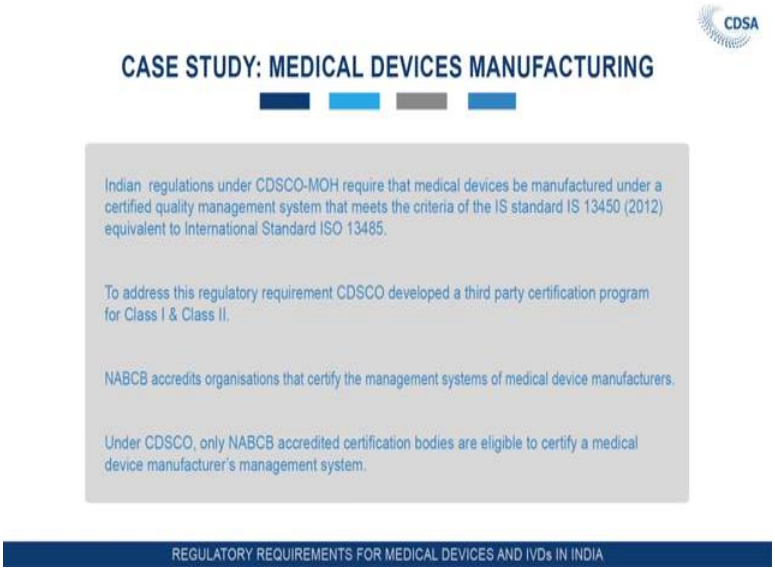

The case studies medical device manufacturing; in Indian regulations under CDSCO, Ministry of Health require that medical devices be manufactured under certified quality management system that meets the criteria of IS standard IS 13450 2012 equivalent to ISO 13485. So, IS BIS standard IS 13450 is exact replica copy of ISO 13485. So, you can walk into the BIS office in Delhi or their branches enhanced for IS 13450 you will get a copy of relevant ISO 13485.

To address regulatory requirements CDSCO developed a third party certification program for class 1 and class 2 medical devices. Now why I am, these slides are important is that, when we talk about medical devices as in the earlier slides we have said that material devices are not chemical entities and they do not have any standardized testing procedure.

So, standards and quality have to be built in that product right from the very beginning; that is the reason we have got all this is ISO certification scheme and auditing etc., so that the ultimate product is what we require and you do not require to test the final product always like a drug.

National accreditation board for certification bodies which is located in Delhi in accredits organizations that certify the management systems of medical device manufacturers. Under CDSCO only NABCB accredited certification bodies are eligible to certify a medical device manufacturers management system.

So, once you go through the ISO 13485 system, at the end of the day, at the end of the certification process your product is actually a standard product.

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Quality assurance, in the medical device industry.

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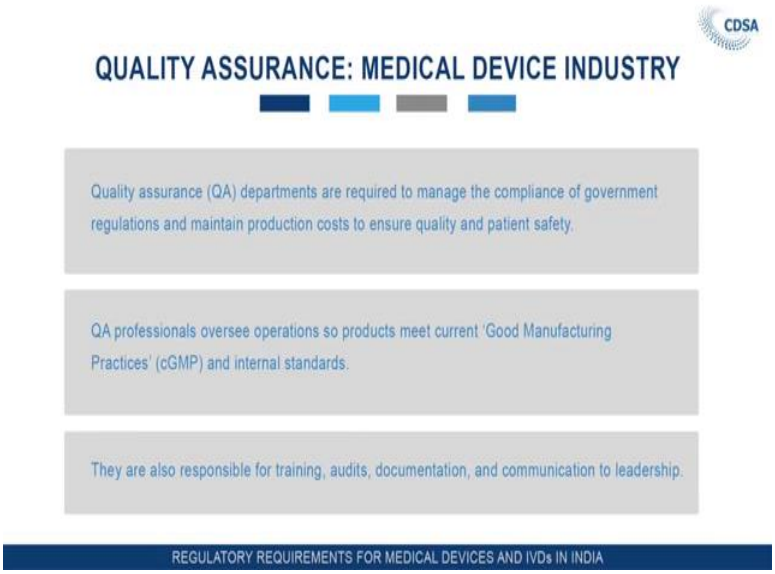

Quality assurance departments are required to manage the compliance of government regulations and maintain production costs to ensure quality and patient safety. QA professionals oversee operations, so product meets current GMP and internal standards.

They are also responsible for training, audit, documentation and communication to leadership.

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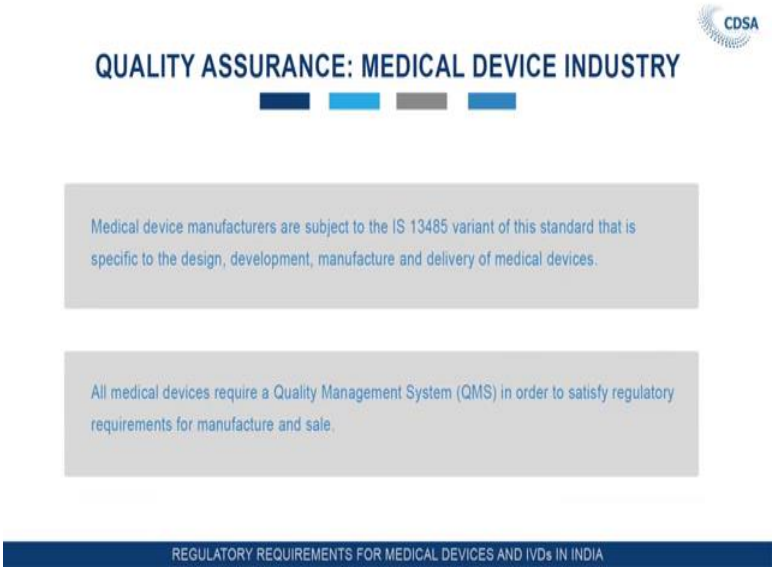

Medical device manufacturers are subject to the IS 13485 variant of this standard that is specific to design, development, manufacture and delivery of material device. All medical devices require a quality management system (QMS) in order to satisfy regulatory requirements for manufacture and sale; and that is the reason why QMS has been adopted by the regulations of medical devices in India.

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Processes of quality assurance; ensure compliance, improve quality, and reduce costs by in centralizing and integrating quality processes, including management and reporting. So, it is a wide ranging concept, right from the very beginning to the end. Audit management, complaint handling and regulatory reporting, corrective and preventive action, risk management, supplier quality management; so whoever is supplying the products to you, are also managed on this QA system.

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Now, we come to testing a medical devices.

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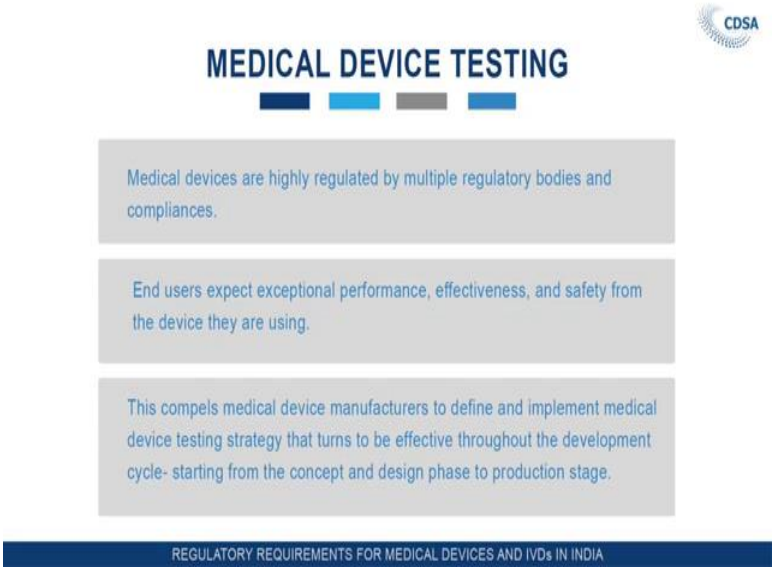

We know that a medical devices are highly regulated by multiple regulatory bodies and compliances. So, there is no one single laboratory at the end of the day that regulates and tests medical devices, it is regulated by multiple regulatory bodies and compliances.

End users expect exceptional performance, effectiveness and safety from the device they are using. This compels medical device manufacturers to define and implement medical device testing strategy that turns to be effective throughout the development life cycle; starting from concept and design phase to production stage.

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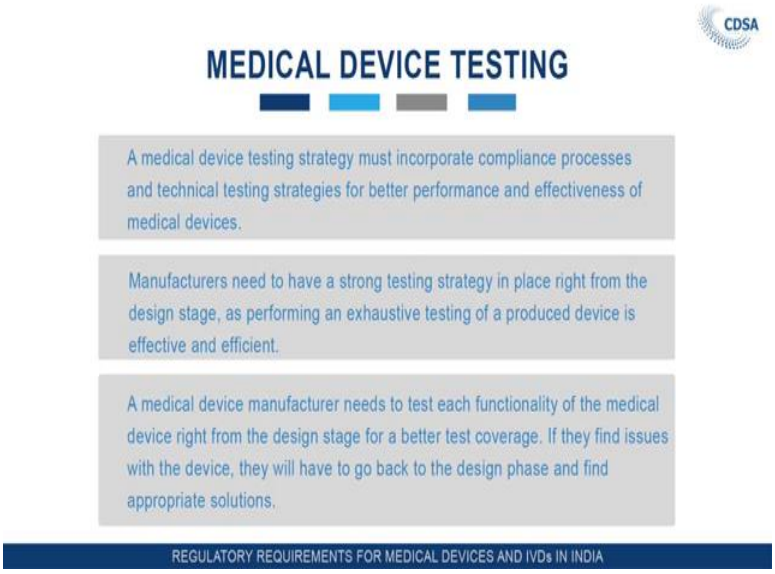

A medical device testing strategy must incorporate compliance processes and technical testing strategies for better performance and effectiveness of medical devices. Manufacturers need to have a strong testing strategy in place right from the design stage, as performing an exhaustive testing of a product produced device is effective and efficient.

A medical device manufacturer need to test each functionality of the medical device right from the design stage for a better test coverage. If they test manufactured device for the functionalities and find issues with the device, it will be non-viable and tedious process to go back to the design phase and find some appropriate solutions for the issues.

Now, this testing, testing of this medical device heading seems to be means no more, if you compare testing of other items that are moving in the market like drugs. As I

mentioned earlier that, medical devices are a curious product; you have to actually build that systems in the manufacturing process that each cycle of medical device is as per the design that is put into it.

So, at the end of the day, you do not need a individual medical device testing to say it is or not. You develop a medical device right from the design stage to the release stage, so that the end user is satisfied that the medical device is being used and is working as it is designed to be.

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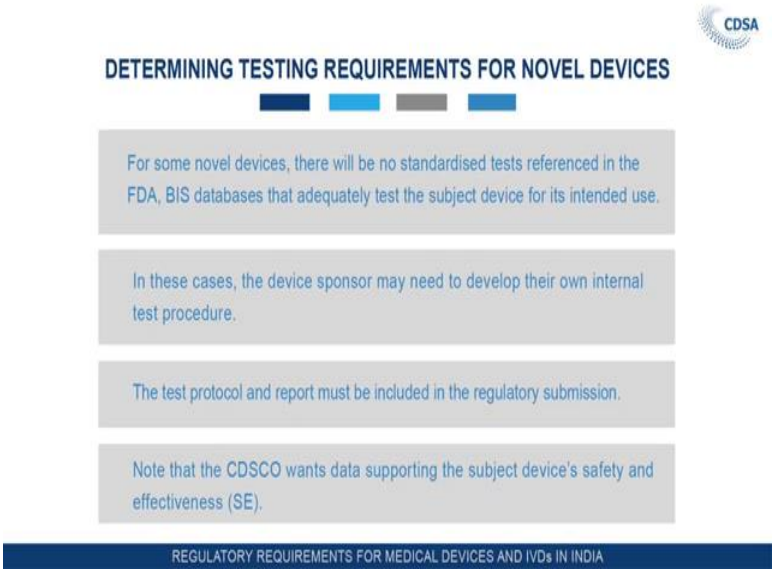

Testing device requirement for this novel devices. This is something different, because novel devices are devices which do not have a predicate; I mean the similar type of device in the market, in this case thing are a bit different. For some novel devices there will be no standards tests referenced in the FDA, BIS databases; that adequately test that the subject device for it intended use. Therefore, the manufacturer has to develop its own testing criteria right from the beginning. And while it is being developed in it is own R & D center.

The test protocol and test report must be included in the regulatory submissions. So, once you submitted, submit to the regulatory FDA or CDSCO for manufacture you have to submit the protocol and test; that is all inclusive right from the very beginning to the end.

Note that the CDSCO wants data supporting the subject devices safety and effectiveness. Safety and effectiveness is very important, because at end of the day the device to be effective in the human body and it is also to be safe for the user.

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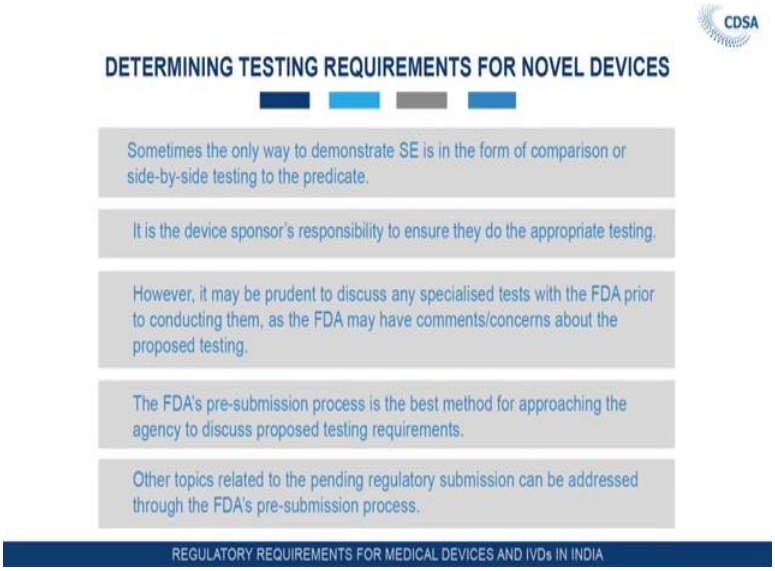

Sometimes the only way to demonstrate SE is in the form of comparison or side by testing to the predicate device which is in the market, similar type of device. It is the devices sponsor's responsibility to ensure they do the appropriate testing. However, it may be prudent to discuss any specialized tests with the FDA prior to conducting them, as the FDA may have comments, concerns about proposed testing.

The FDA pre submission process is the best method for approaching the agency to discuss proposed testing requirements. Other topics related to pending require regulatory require submission can be addressed through the FDA's pre submission process. So, the pre submission process over here is actually the interaction with the CDSCO or the regulator before you submit an application; to discuss with them the best method that is adopted for testing by you and then submit the same to the drug control.

Testing requirement for regulatory submission; in case you want to manufacture a product or a manufacture a product in your plant, what are the requirements. Obtaining CDSCO clearance through the MDR 2017, process requires some form of device testing likely with to be known standard under BIS if not prevailing international standard. So, you have to first get a standard, international standard or standards for that product

before you submit. It might also require other type of verification and validation activities related to the device, design and performance.

So, just simple standards may not work at times. So, you require other type of verification also. I like to do it. These critical items prove the safety and effectiveness of the device and in doing so, demonstrates substantial equipments device; there is simply no way around this. When bringing any product to market especially a medical device where the stakes are much higher, the chances of achieving commercial success increases when you put more thought into the early stages of planning, design and development.

This is needless to add, all medical devices are designed and planned early in the day, before you actually go in for even production in your plant for any reason. Innovators, manufacture to take the time to research all the testing requirements, FDA guidance documents and performance standards that are applied to a device.

Manufacturers regulatory submission should move through the FDA review process with viewer questions; that means, it should be a smooth process in the FDA's channel if everything that you have done regarding the standard and testing etc. is as perfect as possible. While bringing a new product to market especially a medical device where the stakes are much higher.

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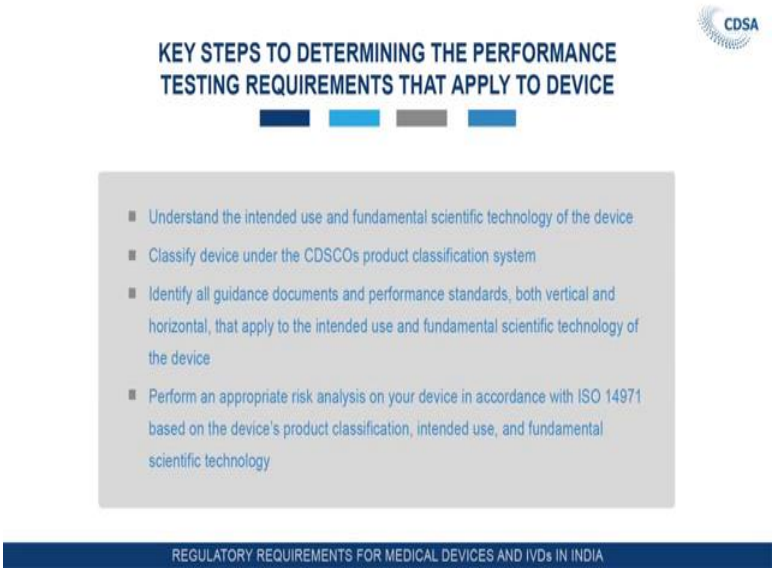

Key steps to determining the performance testing requirement apply to a device; understand the intended use and fundamental scientific technology of the device. This is actually the design stage, early stage. Classify the device that the CDSCO's product classification system.

Identify all guidance documents and performance standards, both vertical and horizontal that apply to the intended use and fundamental scientific technology of the device. Perform an appropriate risk analysis on your device in accordance to ISO 14971 based on the devices product classification, intended use and fundamental scientific technology.

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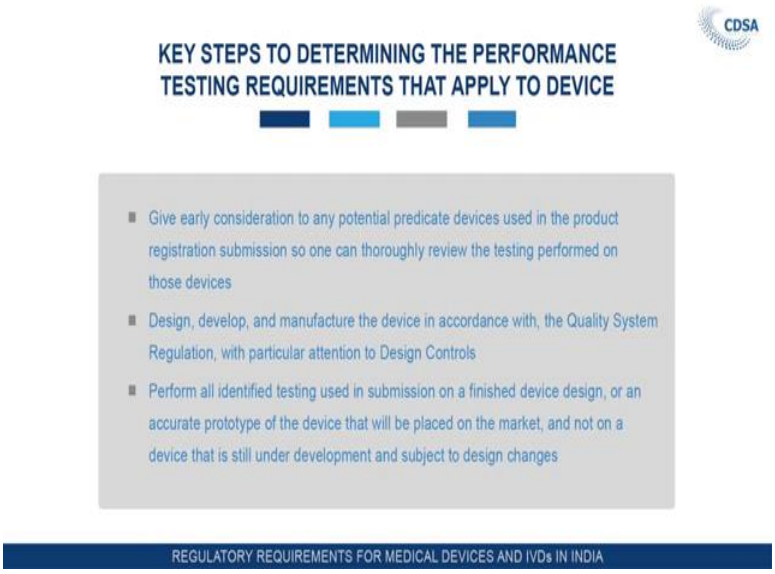

It gives early consideration to any potential predicate device used in a product registration submission. So, one can review thoroughly the testing performed on those devices. Design, develop and manufacture the device in accordance with quality system regulations, with particular attention to design controls. Perform all identified testing used in submission on a finished device design or an accurate prototype of the device that will be placed on the market, and not on a device that will still under development and subject to design change.

The last portion actually means that, whatever data you submit regarding testing and design should be of a product which is actually replica of the product that you want to

put in the market, not a half design or half finished or a R & D product which needs further development on down the line

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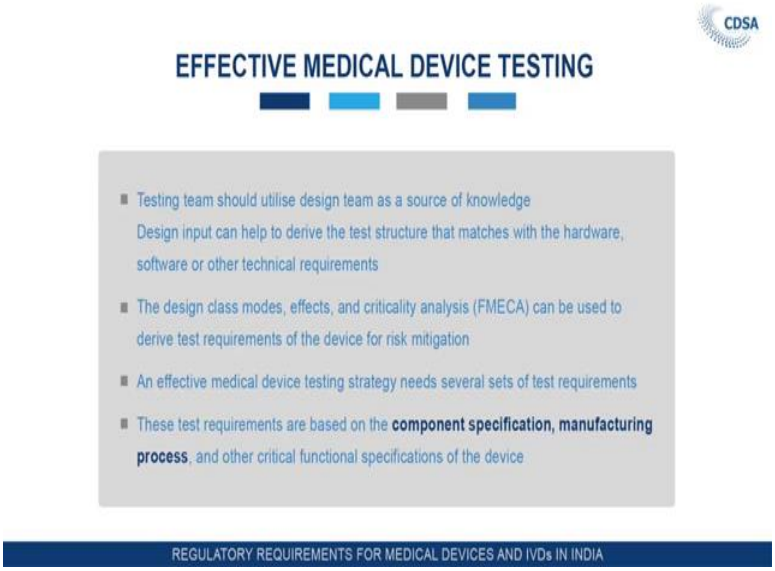

Testing team should utilize design team as a source of knowledge, because testing team is a varied team right from the beginning to the end. And design team is a team which has designed the medical device. Therefore, the design team actually has to have a source to the testing team to have a composite final testing protocol. Design input can help to derive the test structure and that matches with the hardware, software or other technical requirement.

The design class modes, effects and criticality analysis can be used to derive test requirements to the effective resist mitigation. An effective medical device testing strategy needs several sets of test requirements. These test requirements are based on component specification, manufacturing process, and other critical functionality specified to the device.

Test requirements define and describe setup conditions, actions and expected response constraints for each experiment defined in the test steps. These sets of requirements are required to smoothen test implementation as tests are carried out continuously at different stages of the complete manufacturing process, from a component selection to final assembly of the medical device and each stage has different requirements, different parameters to be satisfied.

Not as in the case drugs, where very simple tests are carried out as in process tests and you get down to the final product and test it and release it. In this case each stage has to be tested and until they pass their test, you can not go to the next stage.

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Regular test done for medical devices, testing of active medical devices.

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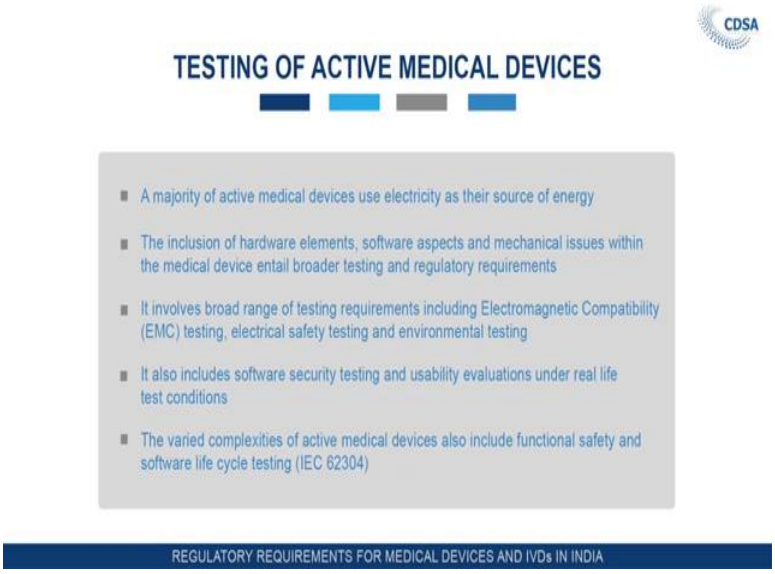

Now, what are active medical devices ? A majority of active medical devices are use electricity as their source of energy. Active medical devices work only when there is an external energy source like, either it can be sunlight or electricity or whatever.

The inclusion of hardware elements, software aspects and mechanical issues within the medical device broader testing and regulatory requirements. So, this slide is actually required for those who want to design a medical device which require electricity; however, none of the medical device which are notified under the law use electricity, therefore this is just a passing reference for knowledge.

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Environmental testing; environmental testing simulates the different climatic condition and mechanical stress that products are exposed during their lifetime. This is akin to your stability testing of drugs, where drugs are put under stress conditions of temperature, humidity and kept for a fixed period of time to find out whether they expire or not. In this case the medical devices are also put through different climatic condition, high temperature, freezing conditions and also mechanical stress; remember these are mechanical items, that the products are exposed to during their lifetime.

Sometimes environmental testing will expose weaknesses in a product's design or performance that could occur in service, particularly at extreme levels. Manufacturers are constantly striving to demonstrate that their products are safe, reliable and compliant in every operational scenario. In general environmental tests can prove the reliability of your product. Manufacturers can demonstrate that your products have the build quality to work perfectly, no matter what the conditions. We have seen in regular life that, there are

certain products of say plastic or rubber with which should stay with you for say at least 3 years; but they deteriorate in 3 year 3 months condition in within 3 year 3 months.

So, those products have not gone, under gone thorough environmental testing of heat and humidity and temperature; and therefore, they deteriorate. So, this should not happen in case of medical devices.

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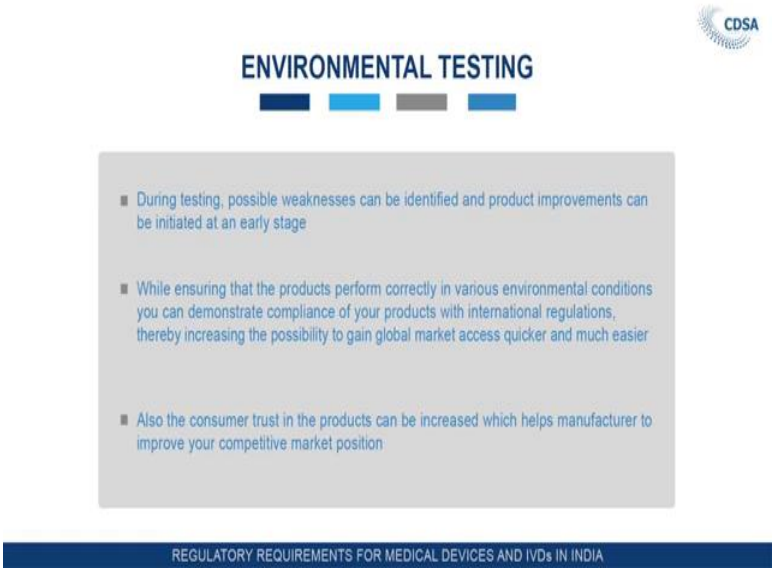

During testing, possible weaknesses can be identified and product improvement can be initiated at an early stage. While ensuring that the products performs correctly in various environmental conditions, you can demonstrate compliance of your product with international regulations, thereby increase the possibility to gain global market access quicker and much easier.

Therefore a product which is designed to be used in India, should be able to perform in a similar manner in a market which is away from India; say the western market or the eastern market, if it is done in different stress conditions. Also the consumer trusts in the product can be increased which helps manufacturer to improve competitive market position.

Testing of non-active medical devices, this is important because all our products which are licensed at the moment are non active medical devices. Maybe very soon we shall be having a few active medical devices; but at the moment most are non-active medical

devices. Broad range of testing including biological, chemical and mechanical and physical testing will be carried out before release.

Medical devices need to get evaluated for chemical characterization, for any components as well as services for analysis for extractable, leachable and chemical residues. Medical devices are also undergoes contamination diagnosis and shelf life studies in addition to microbiological tests such as bio burden, sterility endotoxin LAL tests and biocompatibility tests. These actually these three give you the huge range of parameters that are required to be gone through for testing a medical device.

In the first bullet you see there is a biological, chemical which we already know; the second to mechanical and physical testing are unique to medical devices and should be adhered to very rigidly.

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ISO 10993 is dash 1 is a biocompatibility testing. So, if you are test initially designing a medical device, in the initial stages we have to carry out this particular testing if it is coming into the contact of the human body for a long time of long time like implantable devices. This particular ISO 10993 - 1 use details of how it is to be done.

Now remember, this particular biocompatibility test or other type of test that is in drugs is different from this; because this is in ISO 10993 - 1 and if you catch hold of this ISO, it will guide you how to go about testing for biocompatibility.

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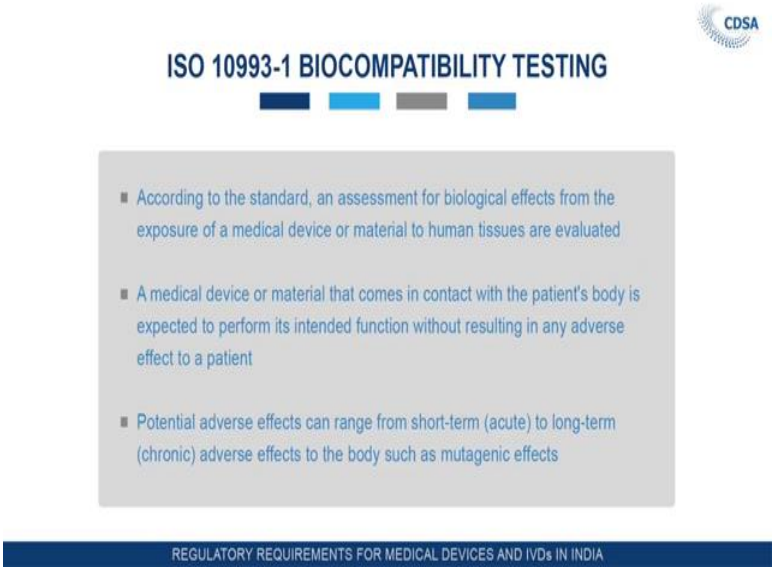

A medical device or material that comes in contact with the patient's body is expected to perform it is intended function without resulting in any adverse effect to a patient. Potential adverse effects that can range from short term acute to long term chronic adverse effects to the body such as mutagenic effects.

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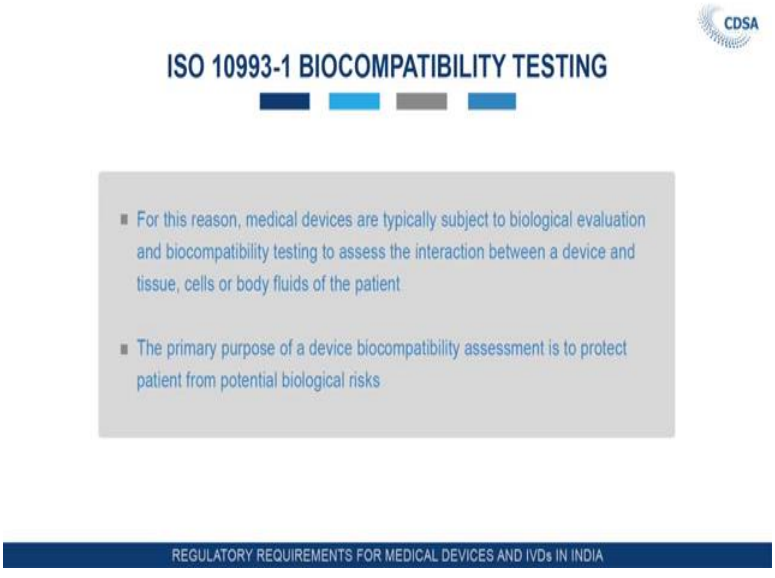

For this reason, medical devices are typically subject to biochemical evaluation and biocompatibility testing to assess the interaction between a device and the tissue cells or body fluids of the patient. The primary purpose of a device biocompatibility assessment

is to protect patient from potential biological risk. So, in case a product is in contact with the human body for a longtime, this particular ISO is helpful for you.

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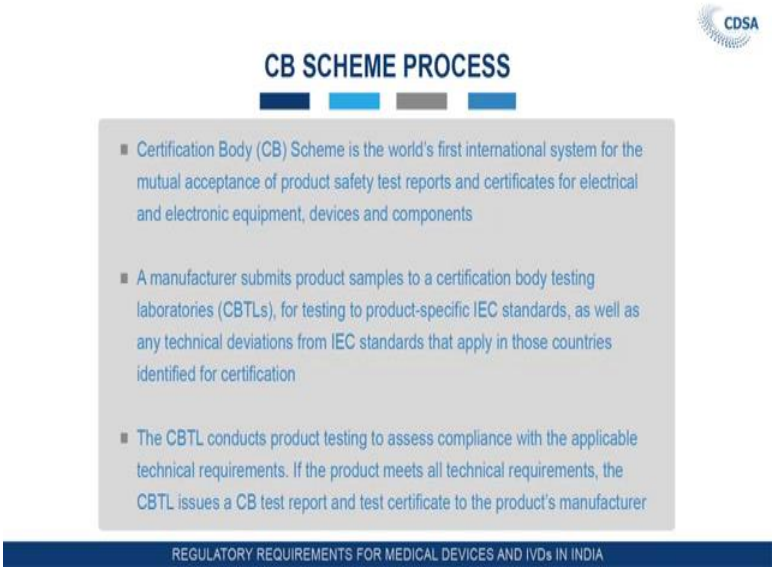

CB chemical scheme process; certification body scheme is the world's first international system for mutual acceptance or product safety test reports and certification for electrical and electronic equipment, devices and components.

Now, this particular is not very important at the moment, because this is of a electronic and electrical equipment. The certification bodies we know they are all available, all over the world.

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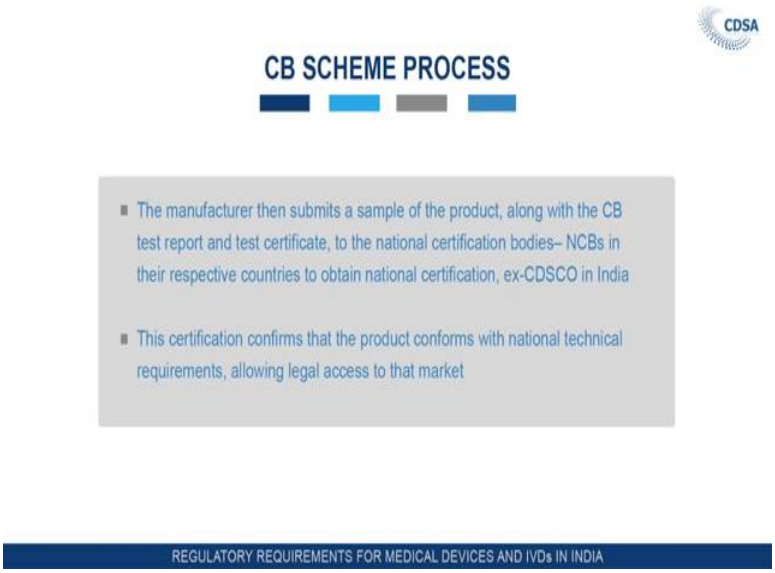

So, if you are manufacturing any certification electronic equipment, this certification body can issue a certificate which is accepted all over the world for your export purposes.

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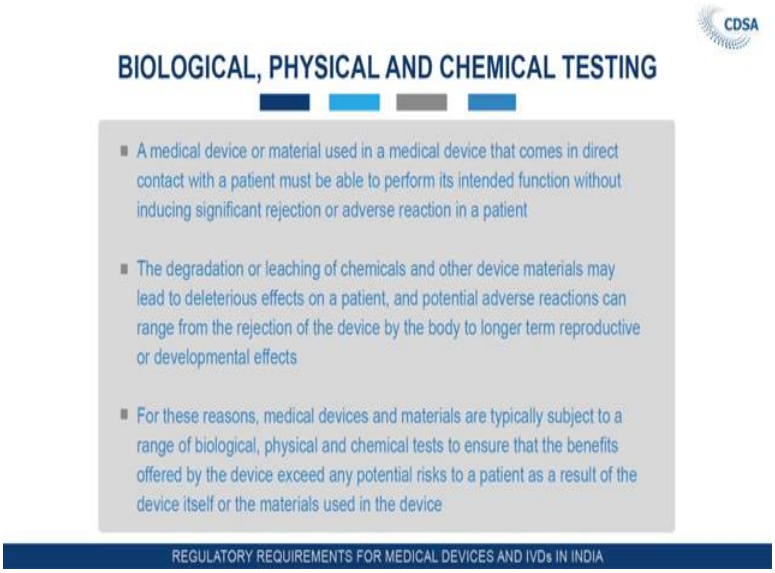

Biological physical and chemical testing; a medical device or material used in a medical device that comes in direct contact with a patient must be able to perform its intended function without inducing significant rejection or adverse reaction in the patient.

Now, in case of drugs what happens is, you can have adverse in your body; however, being a chemical entity, it is treated in different manner all together. But in case of drugs, in case of medical devices; the device can be rejected by the human body with significant discomfort to the patient. So, this particular testing has to be carried out, which is biological, physical and chemical testing.

The degradation or leaching of chemicals, if it is a plastic or a metal which can leach; and other device materials may lead to deleterious effects on a patient and potential adverse reaction can range from rejection of the body of the device by the body to long term reproductive or developmental effects

For these reasons medical devices and materials are typically subject to a range of biological, physical and chemical tests to ensure that the benefits offered by the device exceeds any potential risks to a patient as a result of the device itself or the material used in the device.

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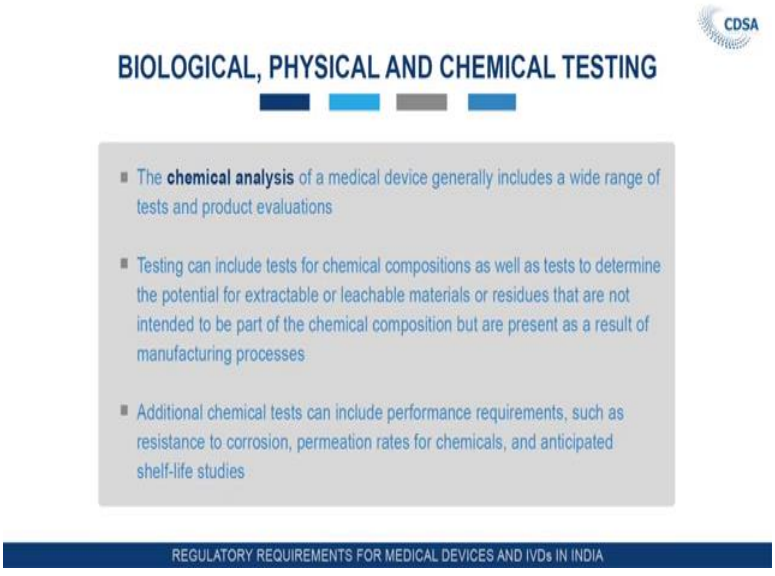

The chemical analysis of a medical device generally includes a wide range of tests and product evaluation. Now, what are the tests that can be done? The tests can include test of for chemical compositions, as well as tests to determine the potential for extractable or leachable material, or residues that are not intended to be part of the chemical composition; but are present as a result of manufacturing process.

Additional chemical tests can include performance requirements such as resistance to corrosion, permeation rates for chemicals, and anticipated shelf life studies.

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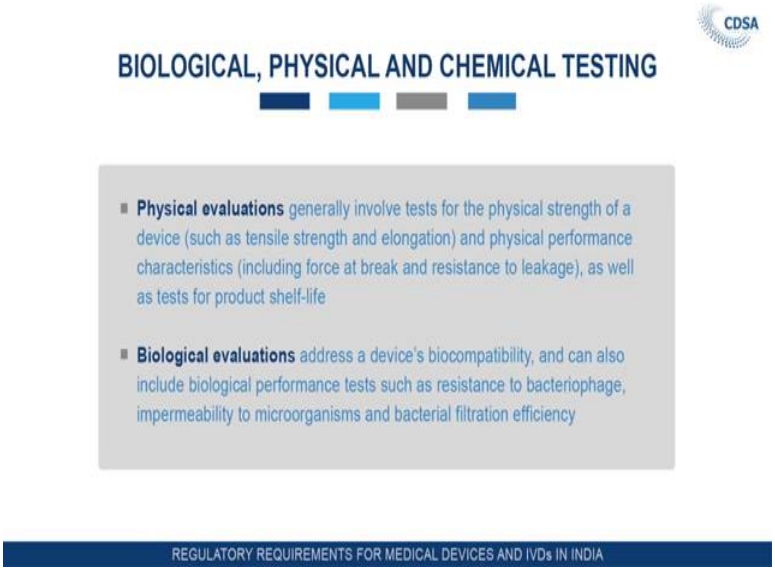

Physical evaluation generally involve tests for the physical strength of a device such as tensile strength and elongation, and physical performance characteristics including force of break and resistance to the leakage as well as tests for product shelf life. Biological evaluation address a devices biocompatibility and can also include biological performance tests such as resistance to bacteriophage, impermeability to microorganisms and bacterial filtration efficiency.

Now, we know from this particular slide that there is a, how the difference between drug and a medical devices start, it is absolutely different. And, you cannot design a testing procedure protocol for a medical device which is applicable all through the range. Medical devices change very fast, they can have different type of construction material, they can be use differently even a same device can be used in two different ways; therefore, testing protocols and methods have to be designed for a particular design by the manufacturer himself, and cannot be codified just like in the pharmacopoeia.

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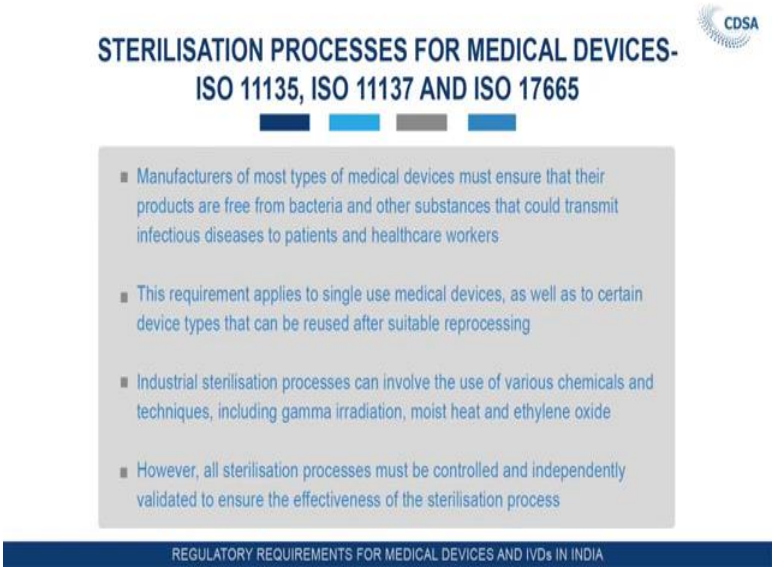

Manufacturers sterilization of medical devices is ISO 11135, ISO 11137, and ISO 17665. Now we know there are certain medical devices which have to be manufactured and so, it is trial like your hard valves or stands or intraocular lenses. Now, in this case the ISO gives a very detailed method of how to carry out sterilisation and its validation. we know what is sterilisation is, pharmacopoeia describes it very clearly; drug, literatures describes them very very nicely.

However, in case of products such as medical devices, ISO sterilisation series comes into play. Manufacturers of most types of medical devices must ensure that, their products are free from bacteria and other substances that could transmit infectious diseases to patients and healthcare workers. This requirement applies to single use medical device as well as so certain devices that can be reused after suitable reprocessing. Industrial sterilisation process can involve the use of various chemicals and techniques; including gamma irradiation, moist heat and ethylene oxide.

However, all sterilization processes must be controlled and independently validated to ensure the effectiveness of the sterilization process. This is a huge topic and requires separate treatment in a presentation. So, sterilization, if you want to understand very clearly how to go about it; those are the ISO numbers 1135, 11137 and 17665 which you have to go through and this will actually help you to design a sterilization for a the type of product that you are going to manufacture.

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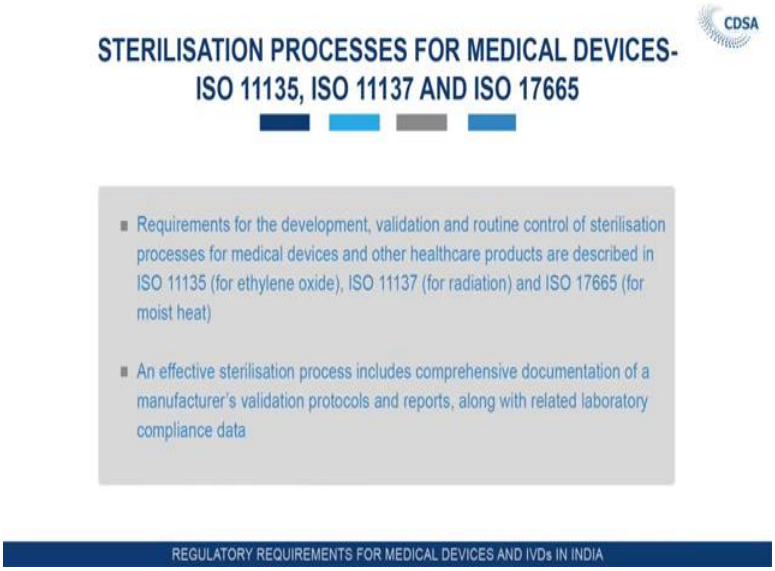

Continuing the sterilization, the requirement for development validation and routine control of sterilization process for medical devices and other healthcare products are described in ISO 11135 for ethylene oxide, ISO 11137 for radiation, and ISO 17665 for moist heat that is in moist sterilizers. An effective sterilization process includes comprehensive documentation of a manufacturer's validation protocols and reports, along with related laboratory compliance data.

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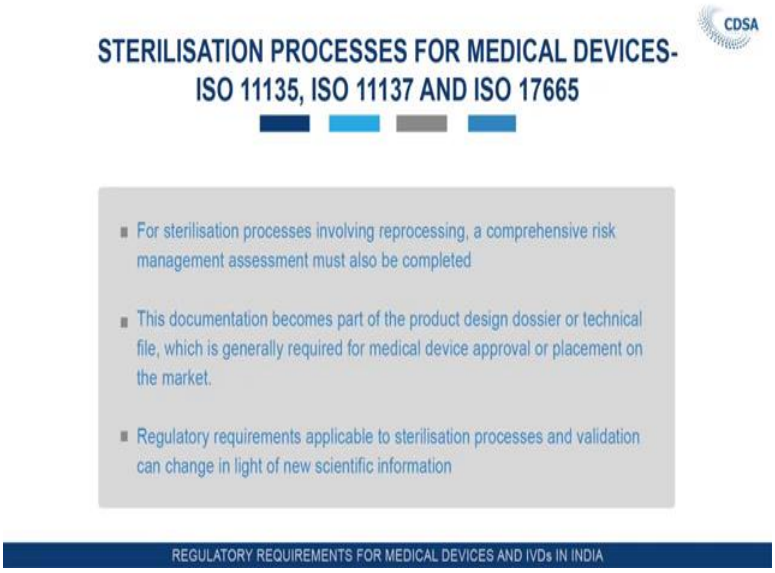

For sterilization processes involving reprocessing, comprehensive risk management assessment must also be completed. Usually sterilization processes are not reprocessed; but in case if they are reprocessed, you have to go through the risk management system again.

This documentation becomes part of a product design dossier or technical file, which is generally required for medical device approval or placement in the market. So, sterilization documentation, you carried out a sterilization of a batch of products or a single product; the documentation of that particular process becomes part of your manufacturing dossier.

Regulatory requirements is applicable to sterilization processes and validation can change in light of new scientific information. Definitely this is very important, you design, you change your design; so maybe your sterilization process will also yeah maybe the time will increase or maybe you have to switch over from radiation to moisture sterilization. So, that depends on the requirement of your product.

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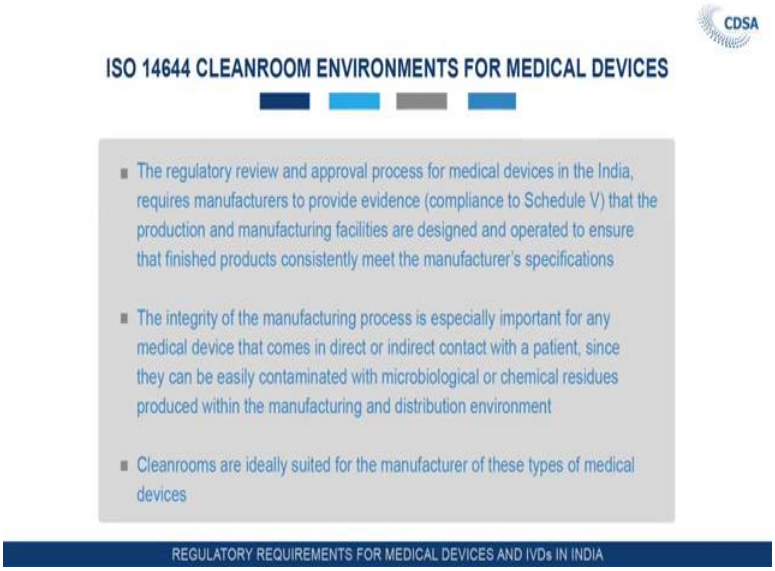

ISO 14644 is clean room environment for medical devices. Some of the medical devices as mentioned earlier are required to be manufactured sterile and as sterilized, so for these items you require a clean room. The regulatory review and approval process for medical devices in India, requires manufacturers to provide evidence compliance to schedule 5 that their production and manufacturing facilities are designed and operated to ensure

that the finished products consistently meet the manufacturer's specifications. So, if a product, final released product is sterile; then it should be sterile product after product batch after batch as you keep on manufacturing, even today after 3 years it should be same.

The integrity of the manufacturing process is especially important for any medical device that comes in direct or indirect contact with a patient. Since they can be easily contaminated with microbiological or chemical residues produced within the manufacturing and distribution environment. Clean rooms are ideally suited for the manufacturer of these types of medical devices.

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Cleanrooms are enclosed and environmentally controlled spaces in which temperature, humidity, pressure and contaminant levels are kept within strict limits. The controlled environment provided by a clean room helps to ensure that products remain under controlled contamination levels throughout the production process thereby reducing potential risks to patients.

Appropriate clean room design, and implementation of personnel policies and procedures that control work within the clean room environment are critical for the production of safe devices.

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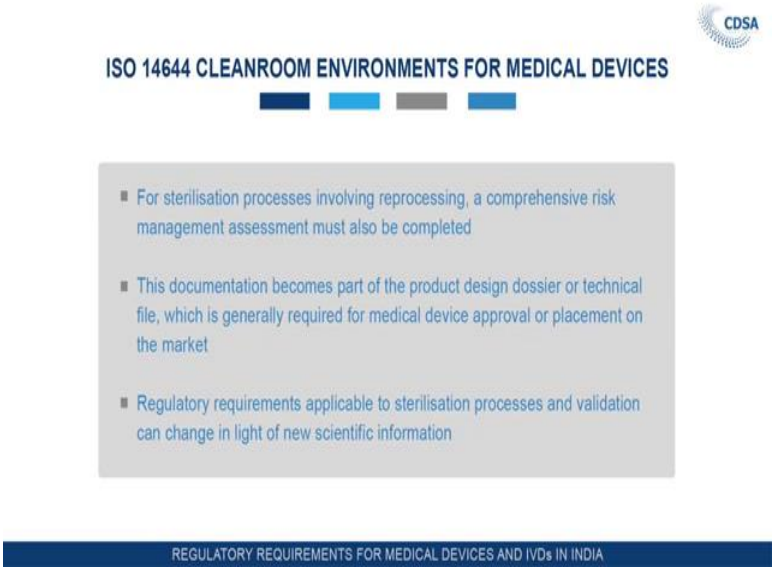

This is all, this particular ISO 14644 is important for the people to understand that clean room operations is so important and this is also being mentioned in the quality management system (QMS) in Medical Devices Rule 2017.

And each this clean room operation is also different complete set of presentations to tell you; how to work in the clean room, how to introduce a product in the clean room, how to clean a clean room and things like that, because ultimately at the end of the day this is also a part of your testing.

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Clean room environment used for production of medical devices are expected to the design specification detailed in ISO 14644 - 4 cleanrooms and associated controlled environments, part 4 design construction and start-up, and ISO 16 644 - 5, cleanrooms and associated controlled environment part 5 operations.

So, ISO 13485 is the mother ISO; however, if you have to manufacture a clean operation, you have to go through all these ISO's again. The control of microbial contamination in cleanrooms is expected to meet the requirements of ISO 14698, clean rooms and associated controlled environments, bio contamination control, as well as good manufacturing practice GMP guidelines schedule 5.

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Conclusion first voluntary standard means manufacturer may not require to comply for regulatory approvals. So, voluntary standards are those standards which may not be required to comply with regulatory. So, you can have, if the voluntary requirements required to have say 20 standards, you can have 22 standards 2 extra voluntary standards which will not be required for regulatory approvals; but you can do it for the betterment of your product.

Mandatory standards require total compliance for product approvals and marketed in India. So, mandatory standards are those standards which are required, now these mandatory standards are reference in ISO actually in QMS system it is 13485. However,

once you comply with 13485, you have to go through all the other ISO standards which have been mentioned in this presentation, which becomes mandatory.

Second manufacturers need to pre discuss with experts, notified body, and regulatory while choosing standards and testing process.

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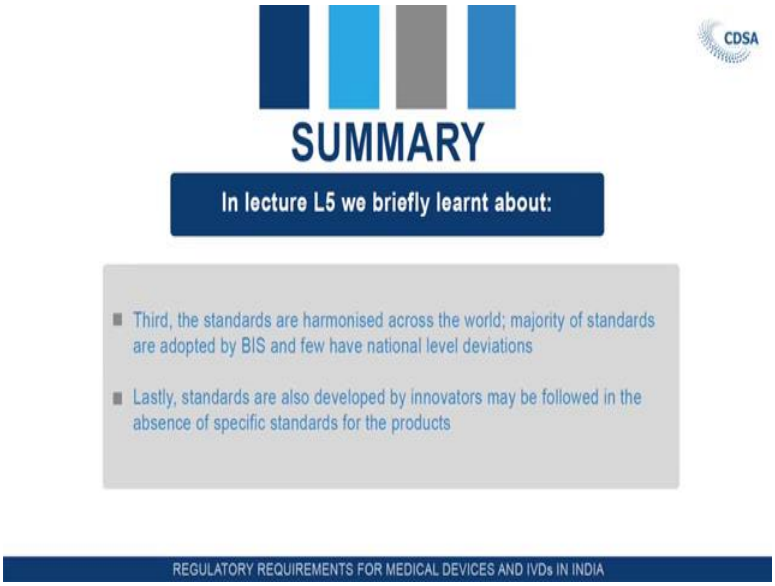

Third is standards are harmonised across the world; majority of standards are adopted by BIS and few are have national level deviations. So, most of the standard that, I have mentioned over here are appropriated by BIS also and it has become Indian standards.

Lastly standards are also developed by innovators and may require to be followed in the absence of specific standards for the products. So, innovative standards are those standards for which there are no standards available in the world. And you in this case also you can take the help of ISO standards in different areas like sterilization and clean room to develop your own standards for the particular innovators product and innovator novel product.

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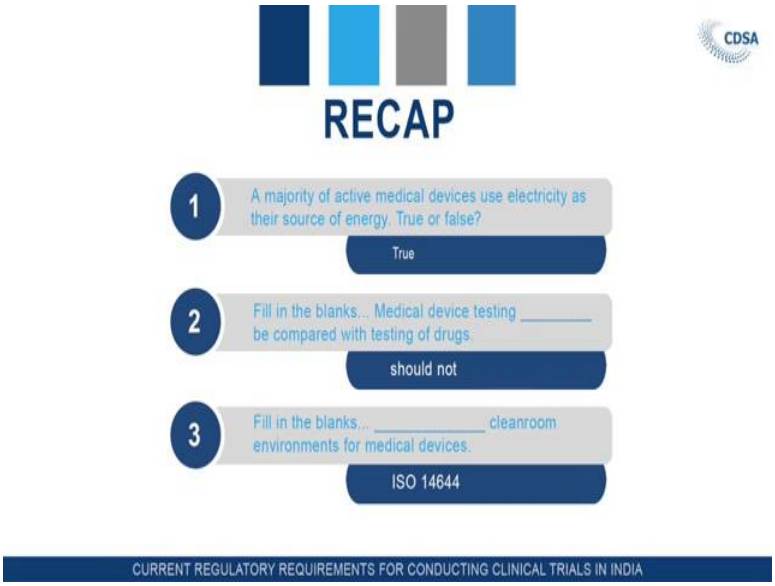

Now, some of the question and answers over the, are over here very simple one; however, you will be getting much more question and answers, you have to submit later on for assessment. So, that is over all.

Thank you very much.