Regulatory Requirements for Medical Devices and IVDs in India

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Lecture-05
C2L05

Dear friends, again welcome to Regulatory Requirements for Medical Devices and in vitro diagnostic in India lecture 5. Lecture 5 that is the standards of the medical devices quality assurance and testing. This lecture will be given by mister Malay Mithra deputy drugs controller, former deputy drugs controller having lot of experience and knowledge about the medical device regulation and vitro diagnostics.

So, in this lecture you will understand what is the standard as you know the 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 specification?

In the standards you will understand the medical devices, the standards can be established a wide range of the specification for the product, process and services. The standards are essentially divided into horizontally standards and vertically standards. What we 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 that is required for the manufacturing of the medical devices.

Similarly, ISO 10993 that is the standards for the biocompatibility, that standard is apply equally to all the medical devices. Also ISO 11135 that is the sterilization, if manufacture has to establish the different sterilization process they have to confirm these standards the part of the standards, other horizontally 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 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 group. If the product is 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 condoms shall confirm these standards that is called the vertically standards for the particular products also like ISO 10555 the 5 that is the standards for I V catheters.

So, these product standards will be consider as a vertically standards for medical devices. So, this type of the clarity or the standards you will discuss in the lectures to be given mister Malaymithra and also recognization of the standards, standards is there what if it is not recognized by the regulatory authority of the country of origin or the particular country there is a no mandatory requirements of the standards.

To have the mandatory requirement, the regulatory authority has to notify has to certify this 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, the Ministry of Health and Family Welfare has made provision that the medical devices shall confirm the standards led by the Bureau of Indian Standards. Bureau of Indian Standard that is the standard setting organization in India established in India and the standards available for the medical devices and that devices are regulate are if regulated, then a BIS standard is applicable for the particular medical devices that is the vertical standards.

Where there is no relevant standards in the BIS or the standards approved by the licensing authority central licensing authority, then other international standards will be applicable. If other international standard is also not applicable in that case the standards of the manufacturers validated standards of the manufacturers approved by the central licensing authority will be consider as the 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 detailed lecture of the 5. So, be concentrate on the lectures whatever the doubts questions you have, you ask the umm experts and we will further clarify the doubts. Thank you very much.

Welcome back again, today our topic is standards of Medical Devices and 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 this will give the very very comprehensive idea about testing of medical devices. Now this is this presentation will it's 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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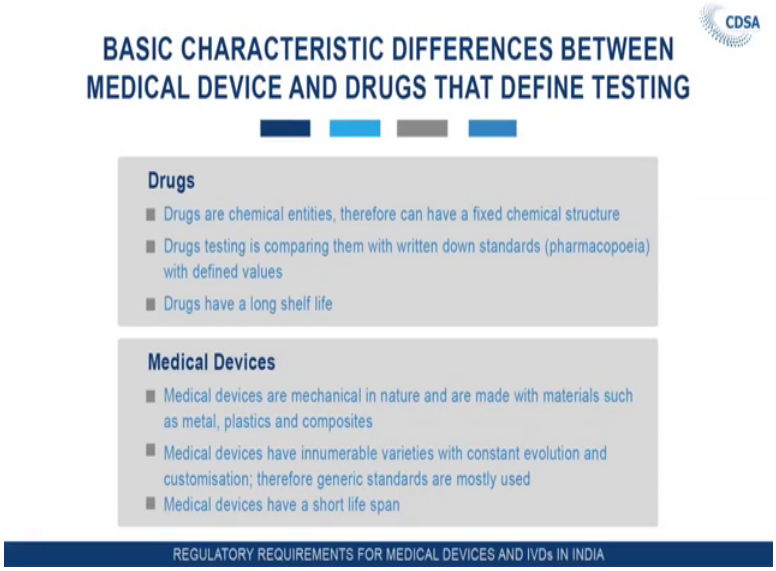

Ah As usual before we start this presentation, I would like to give you a basic characteristic difference between medical device and drugs that define testing. Testing is very easy to understand testing in case of normal items, but in medical device it is something different.

The difference basic difference between medical devices is drugs are chemical in nature chemical entities therefore, can have a fixed chemical structure. Drug testing is compare comparing them written down standards pharmacopoeia and with defined values and drugs have a long very long shelf life this is what basically 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 no well. So, in case of medical devices testing standards cannot be a constant they have to evolve with the product.

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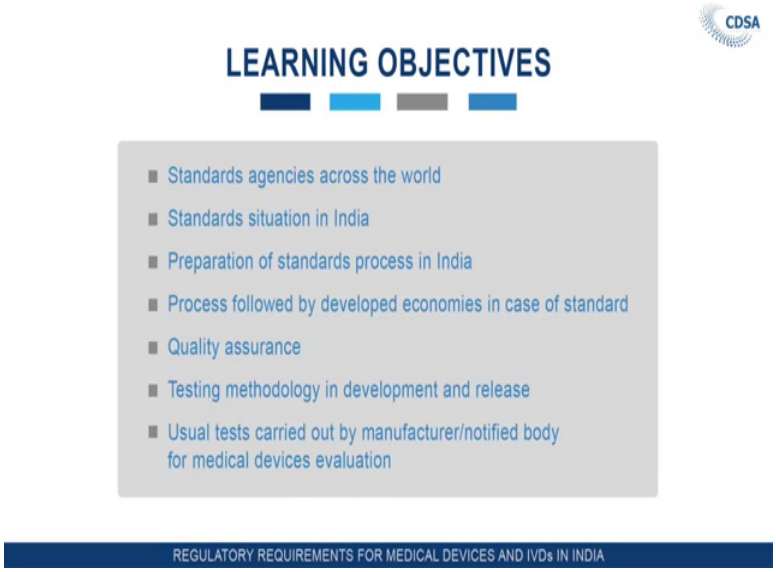

Purpose of this presentation: Standard we will describe the standard agencies across the world, standard situation in India, preparation of standard process in India, process followed by developed economies in case of standard, quality assurance, testing methodology in development and release, usual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

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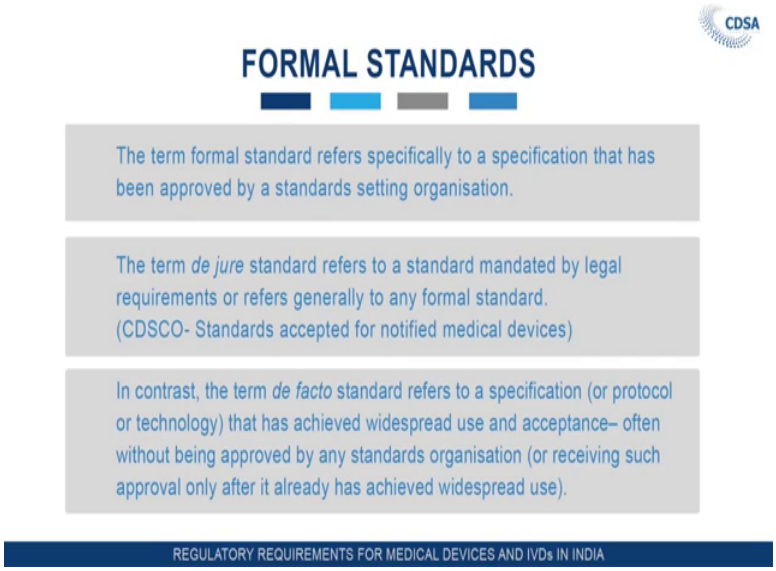

Now, before we go further let us know what are standards. The term formal standard refers specifically to a specification that has been approved by a standard testing organisation that is a formal standard. You can have the informal standard of a product, but in case it is a formal standard, it has been approved by the standard setting organisation. What is standard setting organization? It can it in case of India its BIS or Indian formal commission. The term de jure standard refers to standard mandated by legal requirements or refers generally to any formal standard.

CDSCO standards expected for notified medical devices. In cross the terms de facto refers to a specification or protocol or technology, that has achieved widespread use and acceptance often without being approved by any standards organisation 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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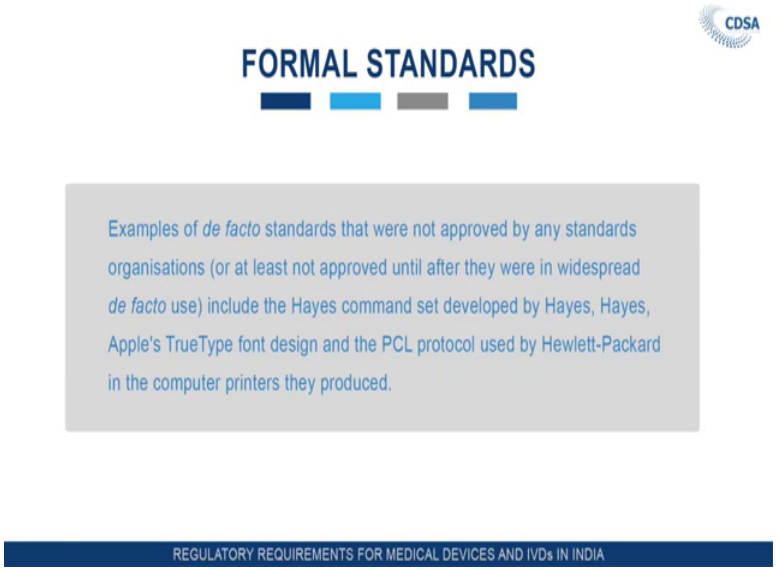

Example of de facto standards that are not approved by any standards organisations or at least not approved until they were widespread de facto use include the Hayes command, set developed by Hayes, Hayes, Apple's True Type font design and the PCL protocol used by Hewlett Packard in the computer printed 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 got this mobile mini USB chargers that standard was developed and is now widespread is in all the mobile phones.

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In case of medical device standards there are two organisations that typically issue international standards. International I am talking about international standards there are two organisation one is your international organisation standardization that is ISO, we know ISO very well through the ISO 9001 which prevalent all over the world and organisation for standards ISO and the International Electrotechnical Commission IEC.

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I the ITU is a treaty based organisation established as a permanent agency of the united nations, in which governments are primarily members although other organisations such

as nongovernmental organisation 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 nongovernmental organisation that develops and publishes international standards on a wide range of subject including medical equipment. This is this maybe news to some of you that ISO is a nongovernmental organization it is not controlled by any government. For the consumer ISO standards ensure the product and services are safe reliable and good quality.

For business, they are strategic tools that reduce costs by minimising the 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 example ISO 13485 establishes the requirement for a quality management system for both the design and manufacture 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 eliminate take risk, the risks in the production and design of the product.

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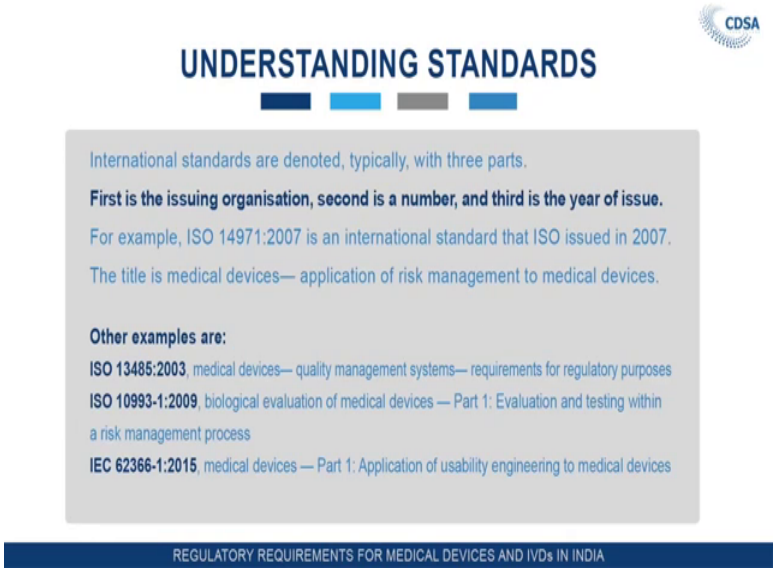

Understanding standards, now you have seen international standards how they are labeled and named. International standards are denoted typically with three parts, the first is the issuing organisation, second the number and the third is the year of issue. For example, ISO 14971 dot 2007 is an international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

Other examples are ISO 13485 dot 2003 medical devices quality management system requirements for regulatory purposes which was issued in 2003. Similarly we have got the other two over there, so once you get a standards, 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 four digits you have to use that for your as a standard.

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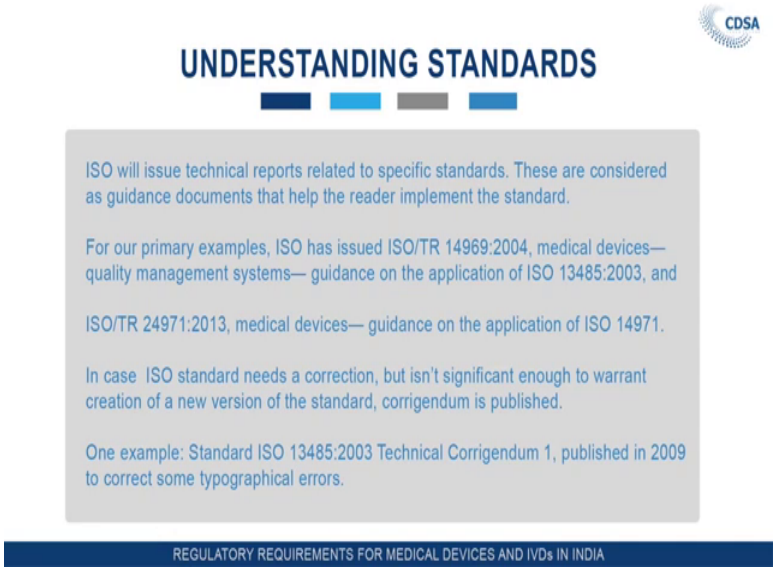

ISO will issue technical reports related to specific standard considered guidance documents that help the reader implement the standard. For our primary example ISO has issued ISO TR 14969 2004 medical device quality management system guidance on the application of ISO 13485. So, this standard ISO TR 149692004 is a standard again which explain how to apply 13485 in your plant.

So, nothing is left the chance anywhere. In case ISO standard needs a correction, but is not significant enough to warrant creation of a new series version of the standard corrigendum is published. For example, ISO 134852003 technical corrigendum one published in 2009 to correct some typographical errors.

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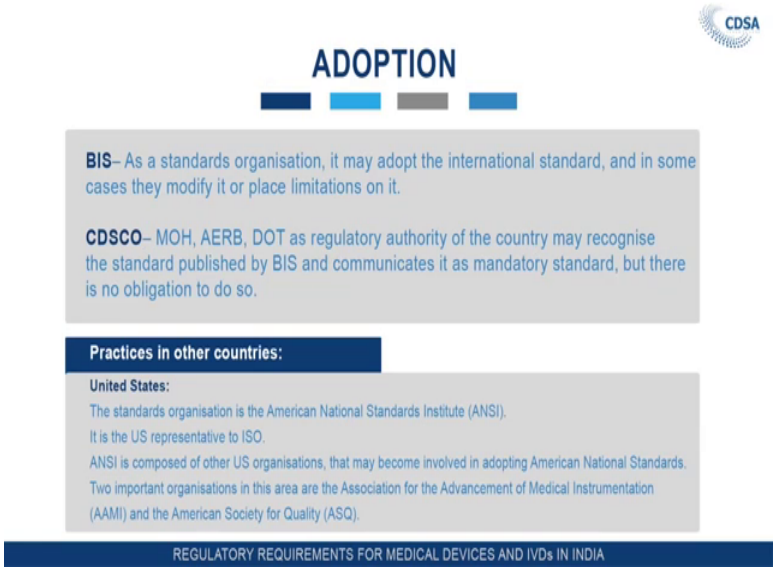

Adoption, now we come to Bureau of Indian standards BIS as a standards organisation may adopt the international standard and in some cases they modify it or place a limitations on it. CDSCO ministry of help, atomic energy regulatory board, DOT as regulatory authority of the country may recognise standard published by BIS and communicate 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 representatives it is the US representative to ISO. So, ISO is represented by in ua USA is represented by ANSI in the ISO organization. ANSI is also composed of other us organisations that may become involved in adopting American National Standards. Two important oraganisations is in the area association advancement of medical instrumentation AAMI and the American Society for Quality ASQ

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

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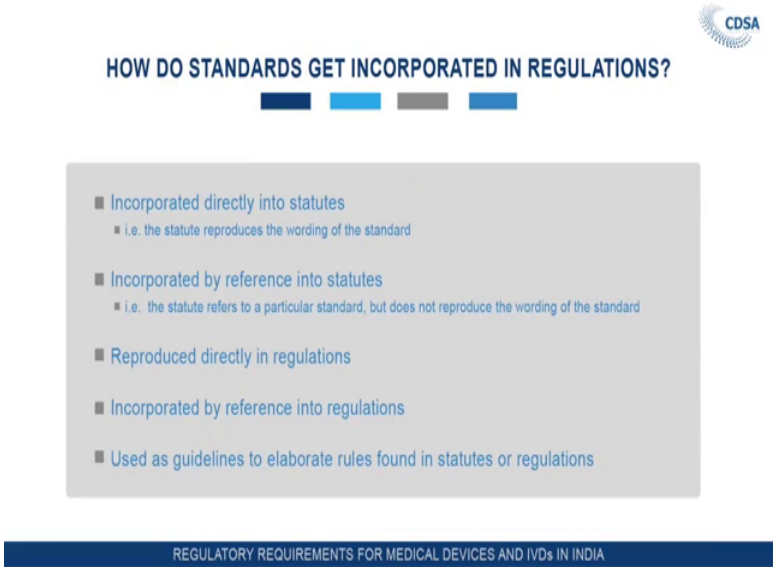

How do the standards get incorporated in? They can be incorporated regulation by various means. This is a simple slide to tell you how they are incorporated. This is not very important because as far as we are concerned medical device whatever is written in ISO in medical device regulation 2017, actually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

It is either directly taken into a the statute, that is the statute reproduces the wording of the standard straight away or it is referred to in the statutes for instance schedule r refers to the ISO standards for syringes. This is reproduced directly in the regulations, incorporated by reference into regulations 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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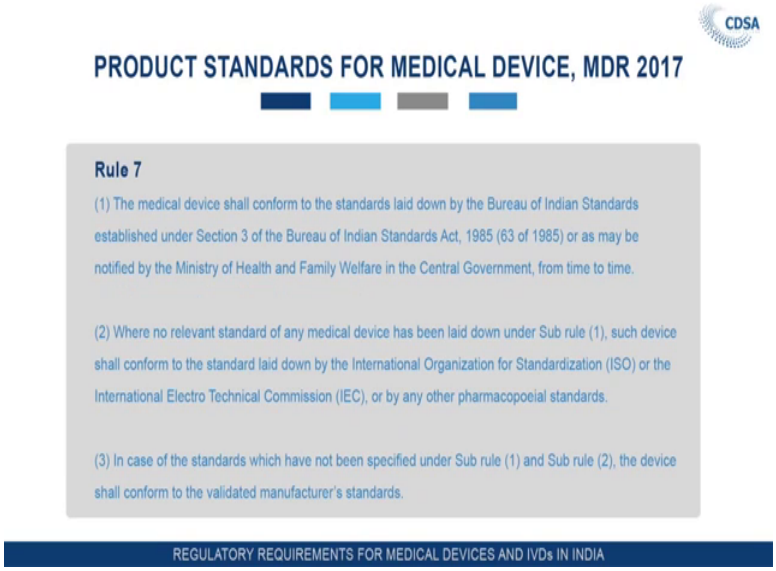

Product standards for medical devices, medical devices rule 2017. Rule 7 of the regulations say, medical devices shall confirm to the standards laid down by the BIS established under section 3 of the BIS act 1985 63 of 1985 or as be notified by the ministry of health and family welfare in the central government in 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 device has been laid down under sub rule 1, such device shall confirm to the standard laid down by the International Organization Standardization ISO or International Electrotechnical 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 which have not been specified under sub rule 1 and sub rule 2, the device shall conform to the validated manufacturers standards.

So, in case there is no standard available anywhere either in BIS or internationally the manufacturer has to make use of own standards and follow it. This third portion 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 of which are not available

anywhere in the world. You have to develop your own standards and how to develop them we will come to subsequent slides.

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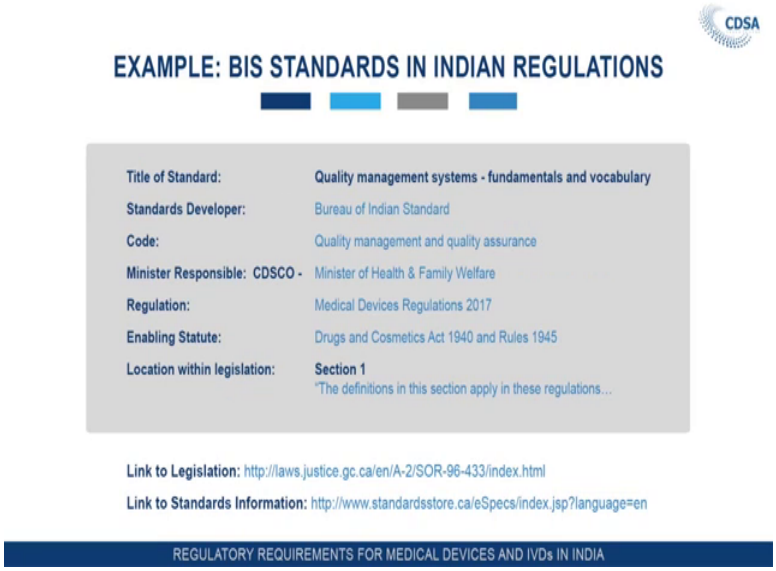

Examples of BIS standards in Indian regulations, that they find mention. Here I have given you two examples one is QMS fundamentals and vocabulary; that standard developer is BIS, code is quality management and quality assurance, minister ministry responsible is ministry of health regulation is the medical devices 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 the then you have got links.

The second one is title of standard is risk management, standard develops by Bureau of Indian standards, code is other standards related to quality, ministry responsible ministry of health, regulation medical devices regulations enabling statute is again DNC 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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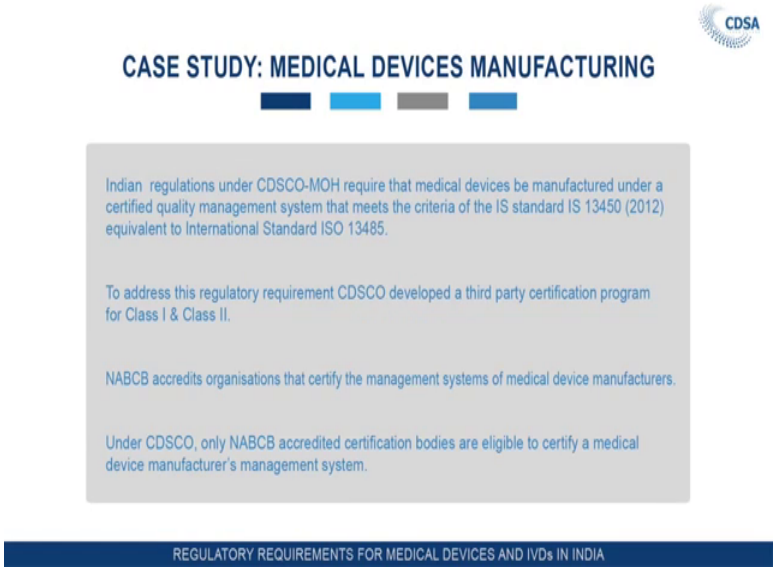

The case studies medical device manufacturing. In Indian regulations under CDSCO ministry of health require that medical devices be manufactured under certified quality management system that meets the criteria of IS standard is IS 13450 2012 equivalent to ISO 13485. So, is BIS standard is 13450 is exactly replica copy of ISO 13485. So, you can walk into the BIS office in Delhi or their branches enhanced for ISO 13 is 13450 you will get a copy of relevant ISO 13485.

To address regulatory requirements CDSCO developed a third party certification program for class I and class II 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 medical devices are not chemical entities and they do not have any standardized testing procedure. So, standards and quality have to be built in that the product right from the very beginning that is the reason we are got all this is ISO certification scheme and auditing etcetera. 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 organisations that certify the management systems of medical device manufacturers. Under CDSCO only NABCB accredited certification bodies are eligible to certify a medical device manufacturer's 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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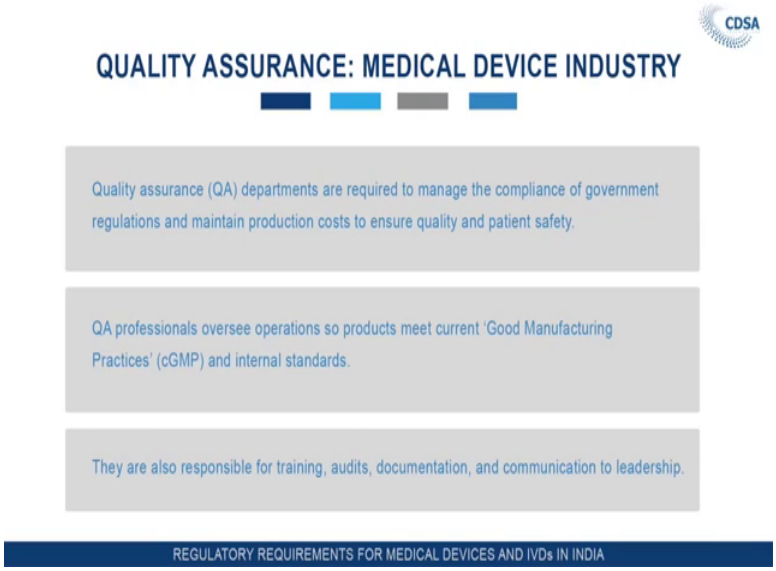

Quality assurance, in the medical device industry. Quality assurance departments are required to manage the compliance of government regulations and maintain production costs to ensure quality and patient safety. QA professionals oversee operations, so product meets current GMP and internal standards. They are also responsible for training, audits, documentation and communication to leadership.

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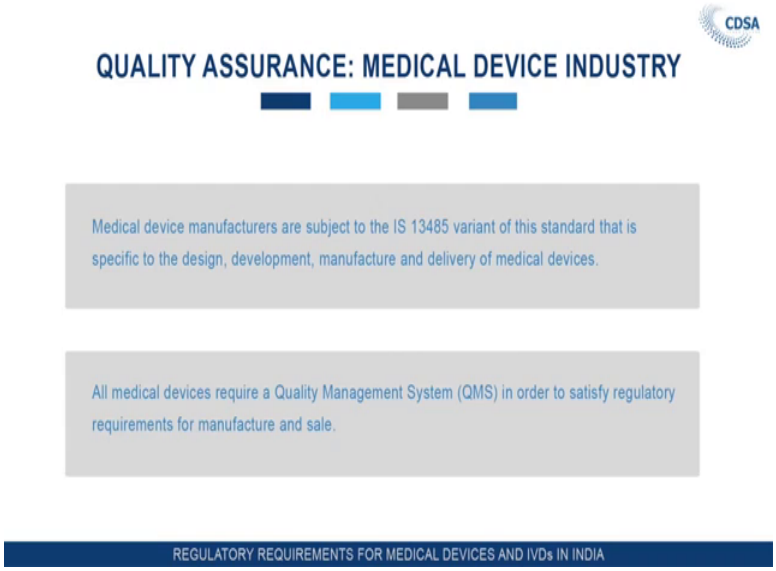

Medical device manufacturers are subject to the IS 13485 variant of this standard that is specific to design development manufacture and delivery material device. All medical devices require a quality management system in order to satisfy regulatory requirements for manufacture and sale, and that is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

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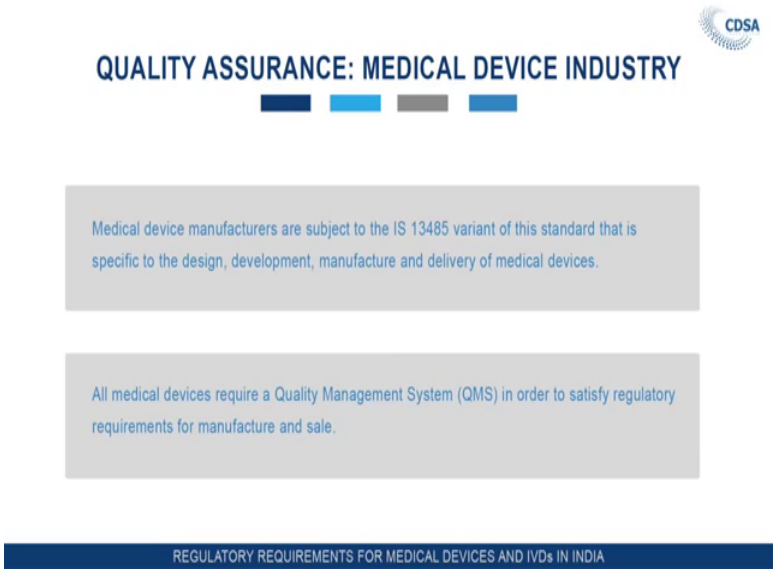

Processes of quality assurance ensure, compliance, improve quality and reduce costs by centralising and integrating quality processes including management and reporting. So, its a wide ranging concept right from the very beginning to the end.

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 by on this QA system.

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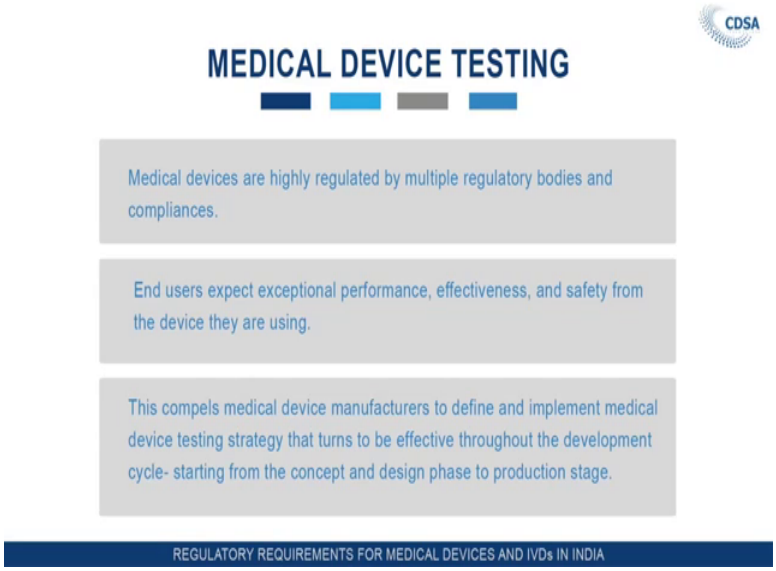

Now, we come to testing of medical devices. We know that medical devices are highly regulated by multi regulatory bodies and compliances. So, there is no one single laboratory at the end of the day that regulates and tests medical devices, it is regulated by multi regulatory bodies and compliances.

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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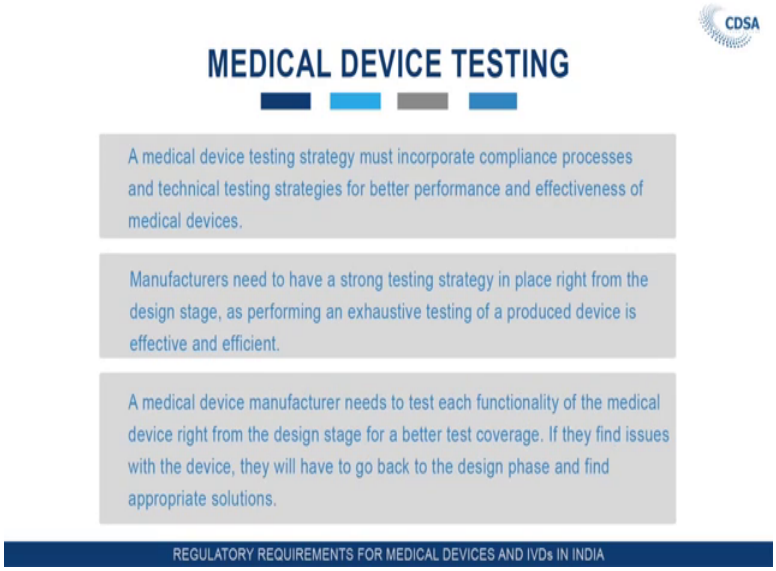

A medical device testing strategy must incorporate compliance processes and technical testing strategies for better performance and effectiveness of medical devices. Manufacturers need to have a strong testing strategy in place right from the design stage, as performing an exhaustive testing of a product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

A medical device manufacturer needs 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 so appropriate solutions for the issues. Now this testing of this medical device heading seems to be misnomer in case 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 to a individual medical device testing to say it's ok 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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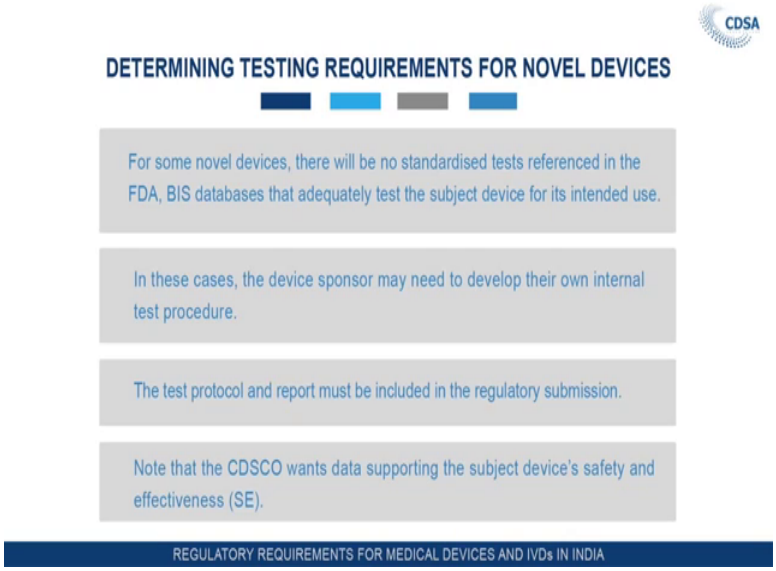

Testing device this novel devices; this is something different because novel devices are devices which do not have do not have a predicate I mean the similar type of device in the market in this case thing are a bit different. For some novel devices there will be no standards tests refer referenced in the FDA, BIS databases that adequately test that adequately test the subject device for it intended use.

Therefore, the manufacturer has to develop its own testing criteria right from the beginning and while its being developed in its own R and D center. The test protocol and test report must be included in the regulatory submissions. So, once it is submitted submit to the regulatory FDA, 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's also to be safe for the user.

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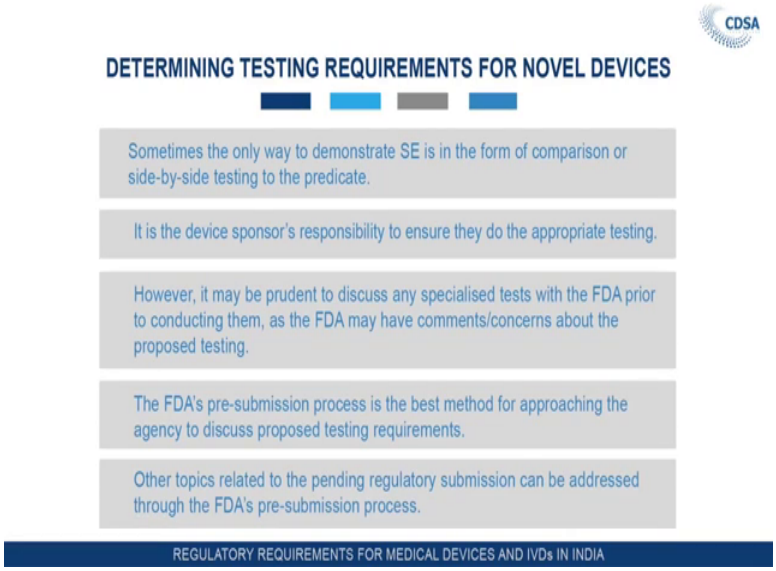

Sometimes the only way to demonstrate SE is in the form of comparison or side by testing to the predicate that is which is in the market similar type device. It is the devices sponsor's responsibility to ensure they do the appropriate testing. However, it may be prudent to discuss any specialised tests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

The FDA as 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 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 of 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, then 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 plan for any reason. Innovator manufacture to take the time to research all the testing requirements, FDA guidance documents and performance standards that are applied to a device. Manufacturer's regulatory submission should move through the FDA review process with viewer questions. That means, it should be a smooth process in the FDAs channel if everything that you have done regarding the standard and testing etcetera is as per is as perfect as possible.

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While bringing a new product to market especially a medical device where the stakes are much higher; 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 under CDSCOs 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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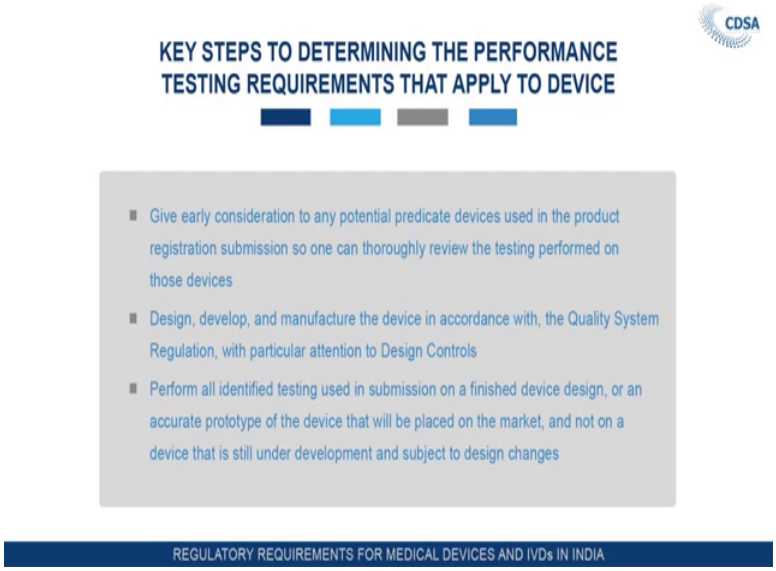

It gives early consideration to any potential predicate device used in a product registration submission, so one can review thoroughly the testing performed on those devices. Design, develop and manufacture the device in accordance with quality system regulations with particular attention to design controls. 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 is 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 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 r and d product which needs further development on down the line.

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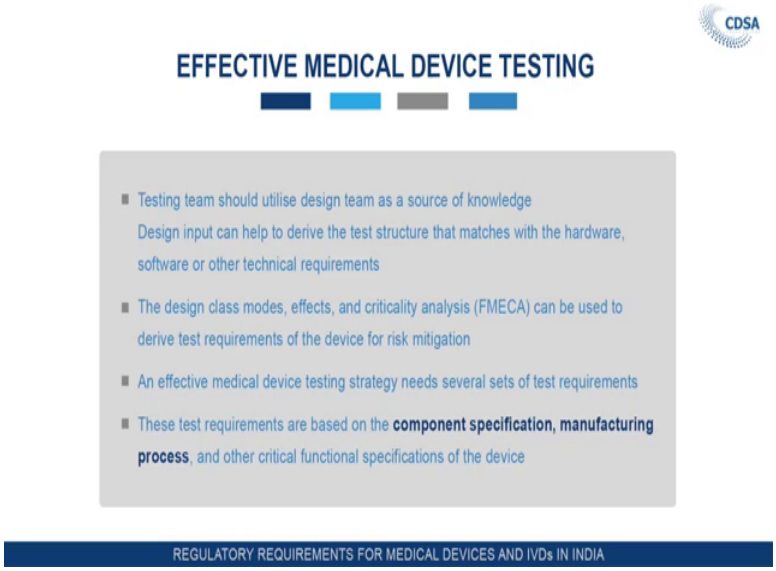

Testing team should utilise design team as a source of knowledge because testing team is a very team right from the beginning to the end and design team is a is a team which has designed the medical device. Therefore, the design team actually has to have a (Refer Time: 32:09) to the testing team to have 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 mode effects and critical criticality analysis can be used to derive test requirements for effective risk 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.

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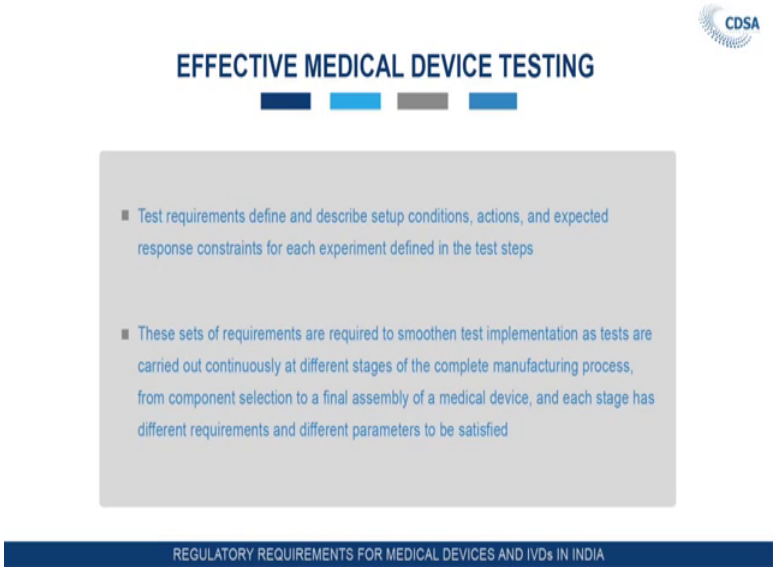

Test requirements define and describe setup conditions, actions and expected response constraints for each experiment defined in the test steps. These sets of requirements are required to smoothen test implementation as tests are carried out continuously at different stages of the complete manufacturing,

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 cannot go to the next stage. Regular test done for medical devices, testing of active medical devices.

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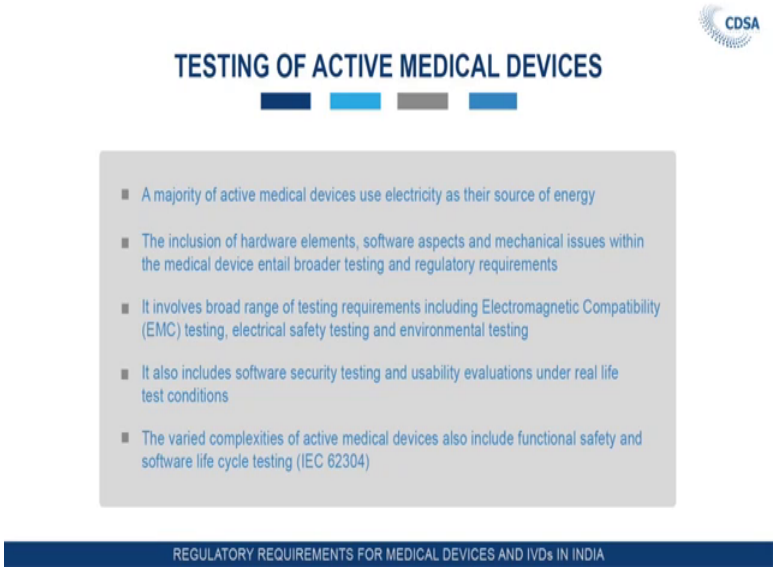

Now, what are active medical devices? A majority of active medical devices are use electricity as their source of energy. Active medical devices work only when there is an external energy source like either it can be sunlight or electricity or whatever. The inclusion of hardware elements software aspects and mechanical issues within the medical device entail 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 (Refer Time: 34:31) 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 products 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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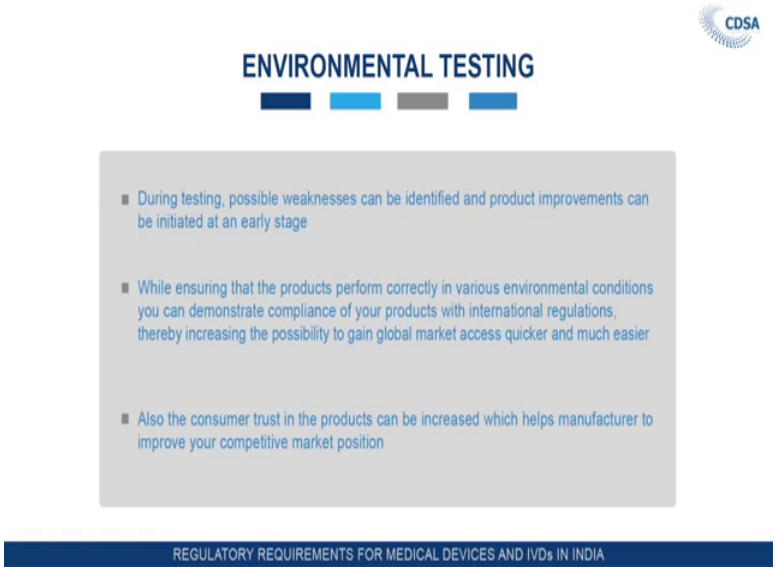

During testing, possible weaknesses can be identified and product improvement can be initiated at an early stage. While ensuring that the products perform correctly in various environmental conditions, you can demonstrate compliance of your product with international regulations; thereby increase the 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.

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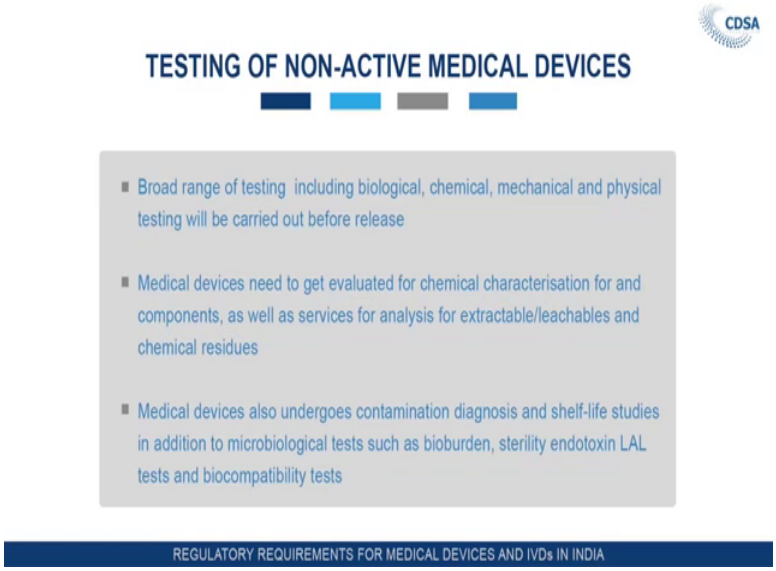

Testing of non active medical devices, this is important because all our products which are licensed at the moment are non active medical devices. Maybe very soon we shall be having a few active medical devices, but at the moment most are non active medical devices.

Broad range testing including biological, chemical and mechanical and physical testing will be carried out before release. Medical devices need to get evaluated for chemical characterisation for any components as well as services for analysis for extractable leachables and chemical residues. Medical devices also undergoes contamination diagnosis and shelf life studies in addition to microbiological tests such as bioburden, sterility, endotoxin, LAL tests and biocompatibility tests.

These actually these three bullets 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 medical devices and should be adhered to very rigidly.

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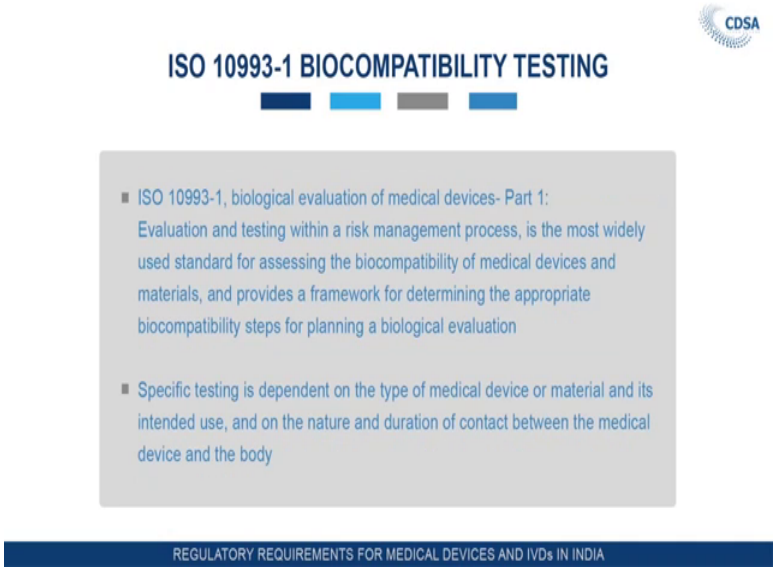

ISO 10993 is dash 1 is a biocompatibility testing, so if you are test initially designing a medical device in the initial stages you have to carry out this particular testing if it is to be if it is coming into the contact of the human body for a long time of long time like in plant able devices, this particular ISO 10993 dash 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 100993 dash 1.

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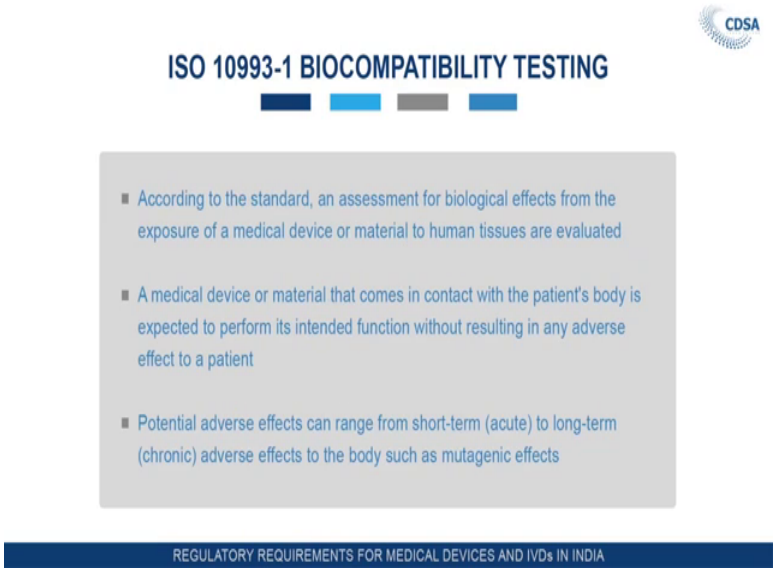

And if you catch hold of this ISO, it will guide you how to go about testing for biocompatibility. A medical device or material that comes in contact with the patient's body is expected to perform its intended function without resulting in any adverse effect to a patient. Potential adverse effects that can range from short term acute to long term chronic adverse effects, to the body such as mutagenic effects.

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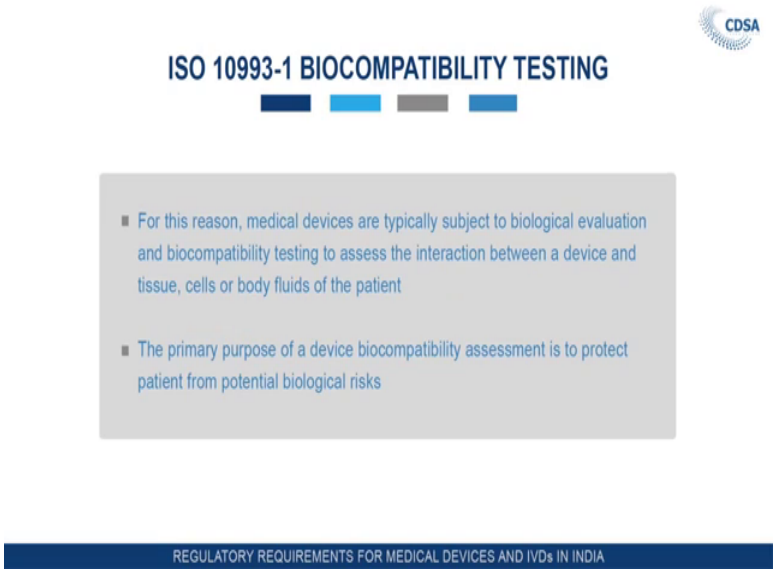

For this reason medical devices are typically subject to biochemical evaluation and biocompatibility testing to assess the interaction between a device and the tissue cells or body fluids of the patient. The primary purpose of a device biocompatibility assessment is to protect patient from potential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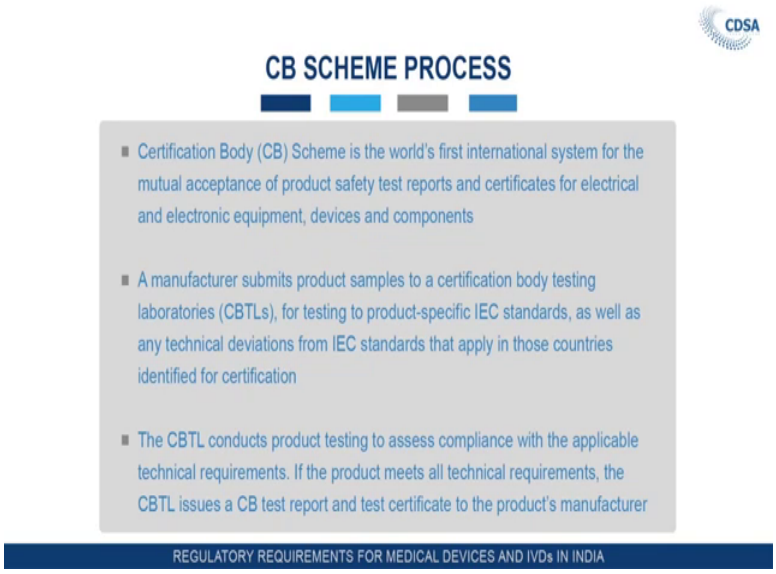

CB chemical scheme process; certification body scheme is the world's first international system for mutual acceptance or product safety test reports and certification for electrical and electronic equipment devices and components. Now, this particular is not very important at the moment because this is of a electronic and electrical equipment.

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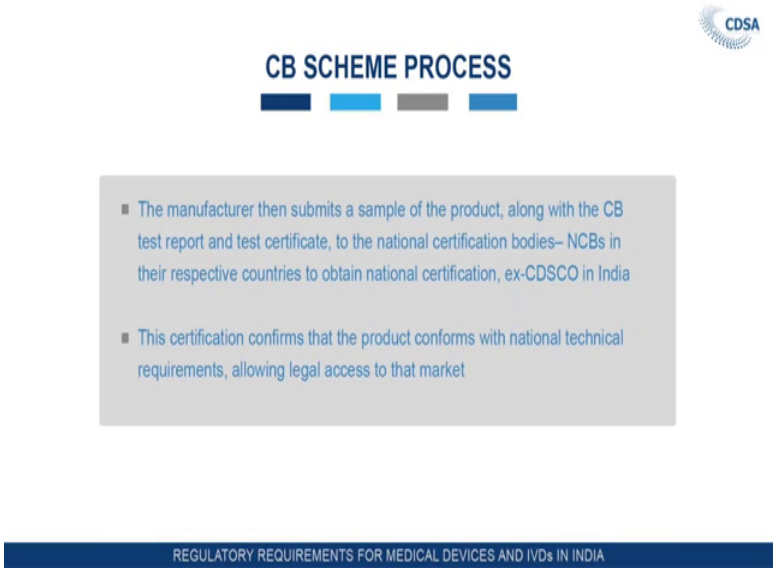

The certification bodies we know they are all available all over the world. So, if you are manufacturing any certification electrical and electronic equipment, this certification body can issue a certificate which is accepted all over the world for your export purposes.

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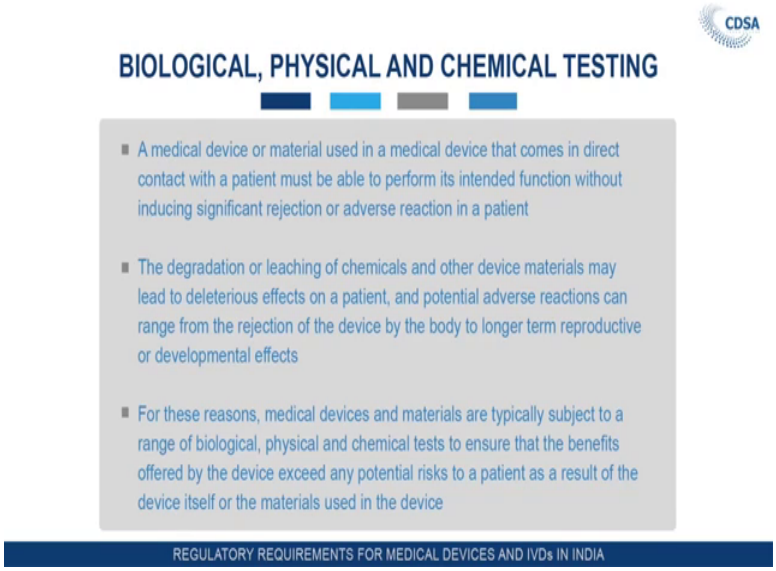

Biological physical and chemical testing; a medical device or material used in a medical device that comes in direct contact with a patient must be able to perform its intended function without inducing significant rejection or adverse reaction in a patient. Now, in case of drugs what happens is, you 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 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 risks.

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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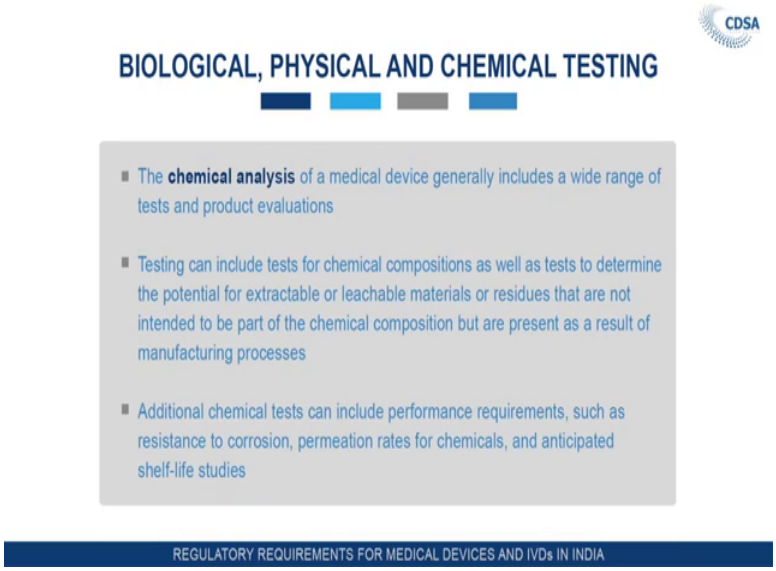

The chemical analysis of a medical device generally includes a wide range of tests and product evaluation. Now, what are the tests that can be done? The tests can include test of for chemical compositions as well as tests to determine the potential for extractable or leachable material or residues that 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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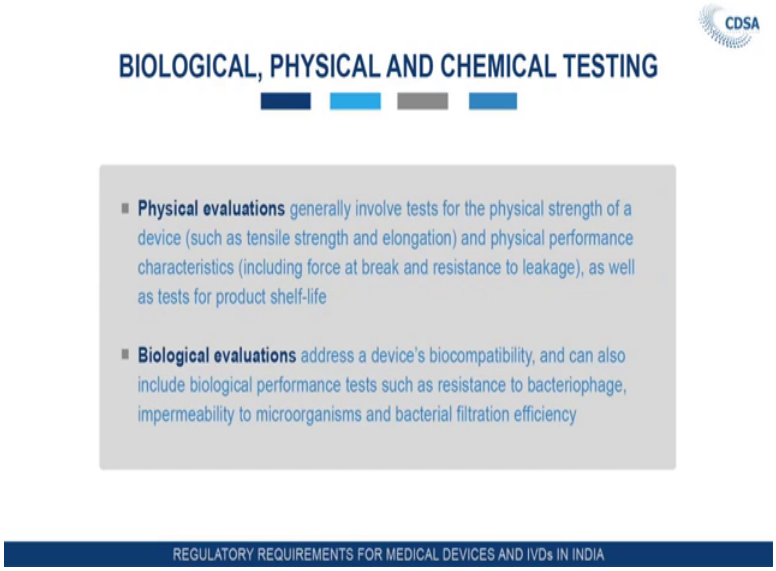

Physical evaluation generally involve tests for the physical strength of a device such as tensile strength and elongation and physical performance characteristics including force of break and resistance to the leakage as well as tests for product shelf life. Biological evaluation address a device's biocompatibility 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's 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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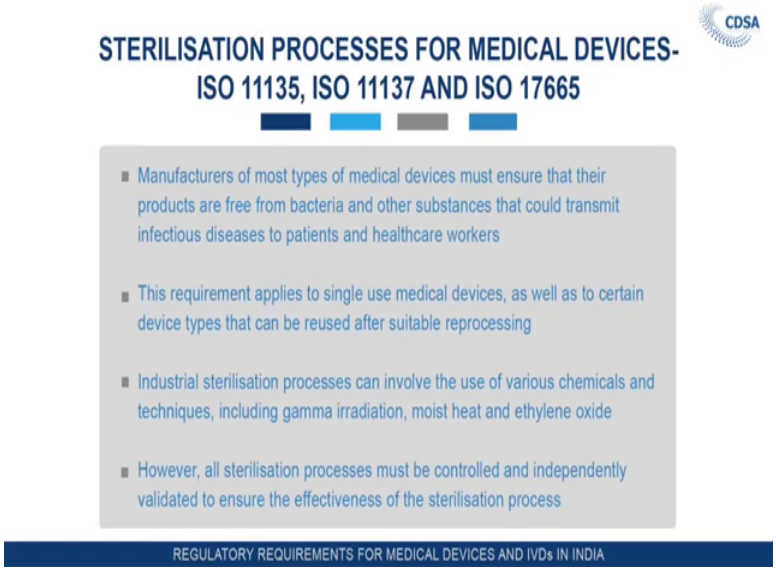

Manufacturers sterilisation of medical devices is ISO 11135, ISO 11137 and ISO 17665. Now, we know there are certain medical devices which have to be manufactured and (Refer Time: 43:19) like your hardwells or stands or intraocular lenses. Now, in this case the ISO gives a very detailed method of how to carry out sterilisation and its validation. We have 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 to 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 sterilisation processes must be controlled and independently validated to ensure the effectiveness of the sterilisation process this is a huge topic and requires separate presentation. So, sterilisation 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 sterilisation for a the type of product that you are going to manufacture.

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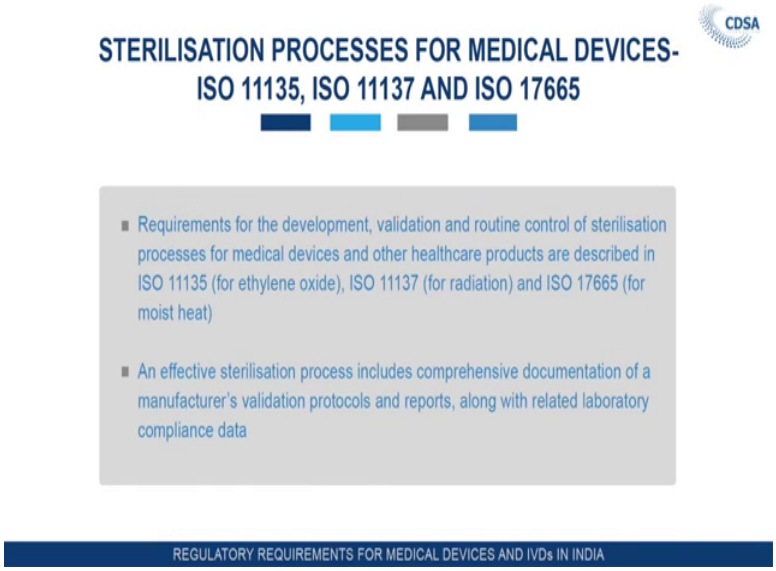

Continuing the sterilization, the requirement for development validation and routine control of sterilisation process for medical devices and other healthcare products are described in ISO 11135 for ethylene oxide, ISO 11137 for radiation and ISO 17665 for moist heat that is in moist sterilizers. An effective sterilisation process includes

comprehensive documentation of a manufacturer's validation protocols and reports along with related laboratory compliance data.

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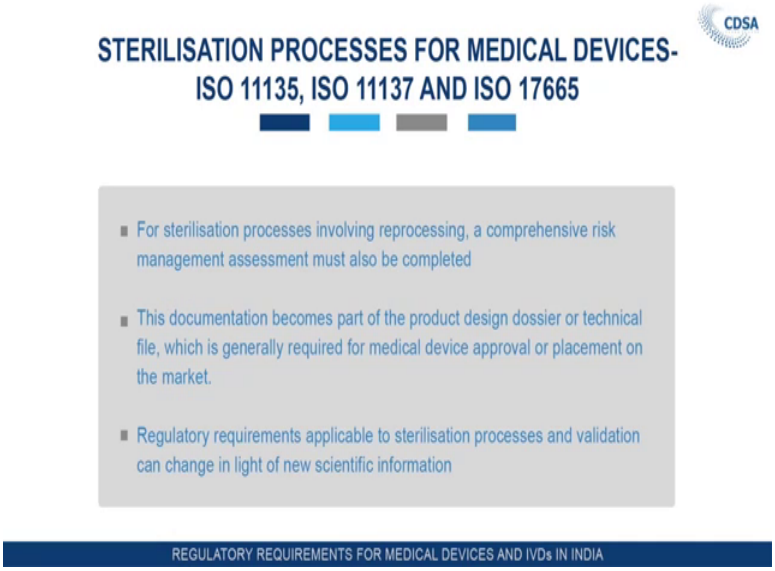

For the sterilisation processes involving reprocessing comprehensive risk management assessment must also be completed. Usually sterilisation processes are not processes are not reprocessed, but in case if they are reprocessed you have to go through the risk management system again.

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 sterilisation of a of a batch of products or a single product, the documentation of that particular process becomes part of your manufacturing dossier.

Regulatory requirements applicable to sterilisation 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 sterilisation process will also yeah maybe the time will increase or maybe you have to switch over from radiation to moisty; moisty sterilisation so, that depends on the requirement of your product.

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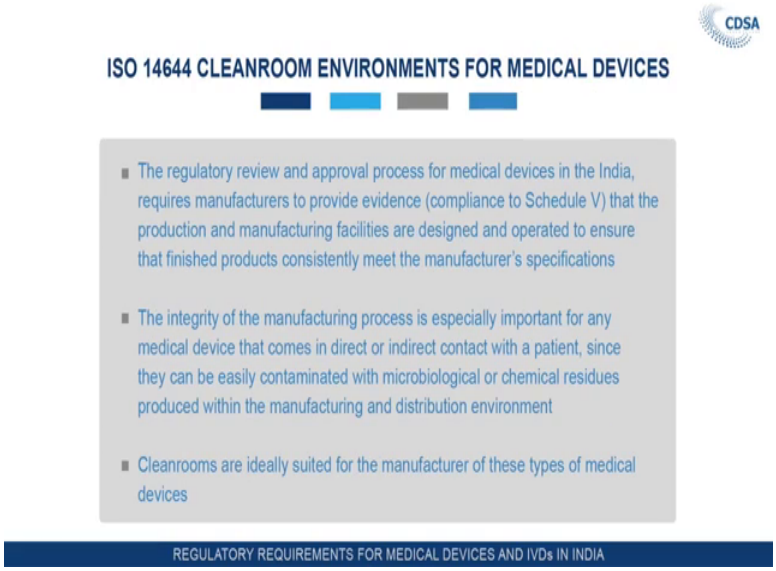

ISO 1614644 is clean room environments for medical devices. Some of the medical devices as mentioned earlier are required to be manufactured sterile and as sterilized. So, for these items you require a cleanroom. The regulatory review approval process for medical devices in India requires manufacturers to provide evidence compliance to schedule V that their production and manufacturing facilities are designed and operated to ensure that the finished products consistently meet the manufacturers specifications.

So, if a product final procedure final released product is sterile, then it should be sterile product after product batch after batch as you keep on manufacturing, even today after three years it should be same. The integrity of the manufacturing process is especially important for nay 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 type of medical devices.

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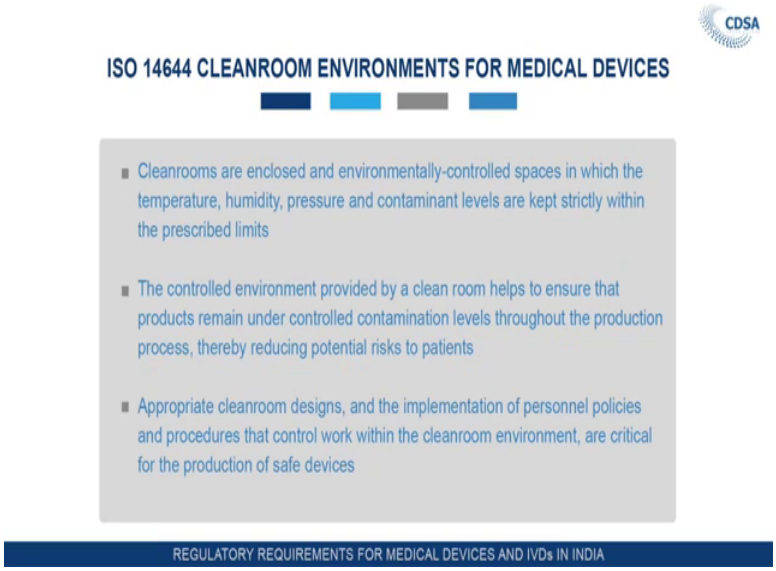

Cleanrooms are enclosed and environmentally controlled spaces in which temperature, humidity, pressure and contaminant levels are kept within strict limits. The controlled environment provided by a clean room helps to ensure that products remain under controlled contamination levels throughout the production process, thereby reducing potential risks to patients. Appropriate cleanroom design and implementation of personnel policies and procedures that control work within the cleanroom environment, are critical for the production of safe devices.

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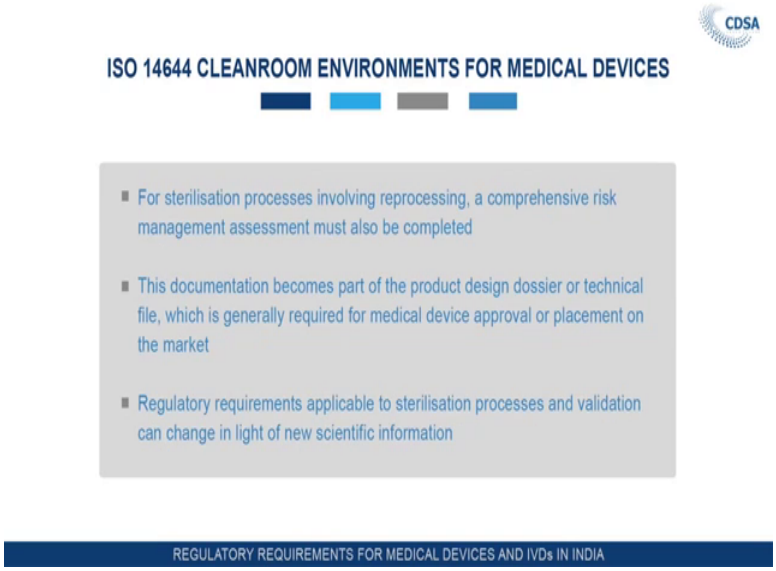

This is all this particular ISO 14644 is important for the people to understand that, cleanroom operations is so, important and this is also being mentioned in the quality management system in medical devices rule 2017.

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

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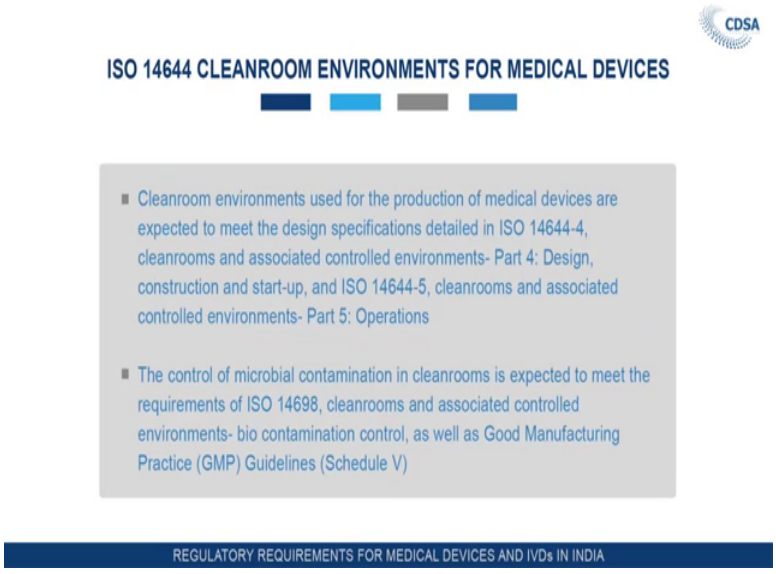

Cleanroom environment used for production of medical devices are expected to meet the design specification detailed in ISO 14644 dash 4, cleanrooms and associated controlled environments. Part 4 design, construction and start up and is and ISO 164 644 dash 5, cleanrooms and associated controlled environment 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 ISOs again.

The control of microbial contamination in cleanrooms is expected to meet the requirements of ISO 14698 cleanrooms and associated controlled environments. Bio contamination control as well as Good Manufacturing Practice GMP guidelines schedule V.

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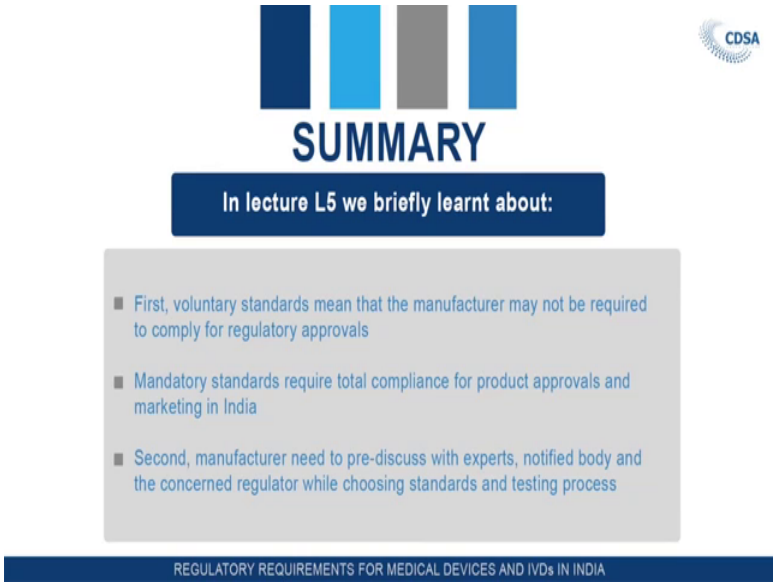

Conclusion, first voluntary standard means manufacturer may not require to comply for regulatory approvals. So, voluntary standards are those standards which may not be required to comply with regulatory. So, you can have if the if the voluntary requirements required to have say 20 standards, you can have 22 standards two 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 1485. 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, manufacturer need to pre discuss with experts notified body and regulatory while choosing standards and testing process.

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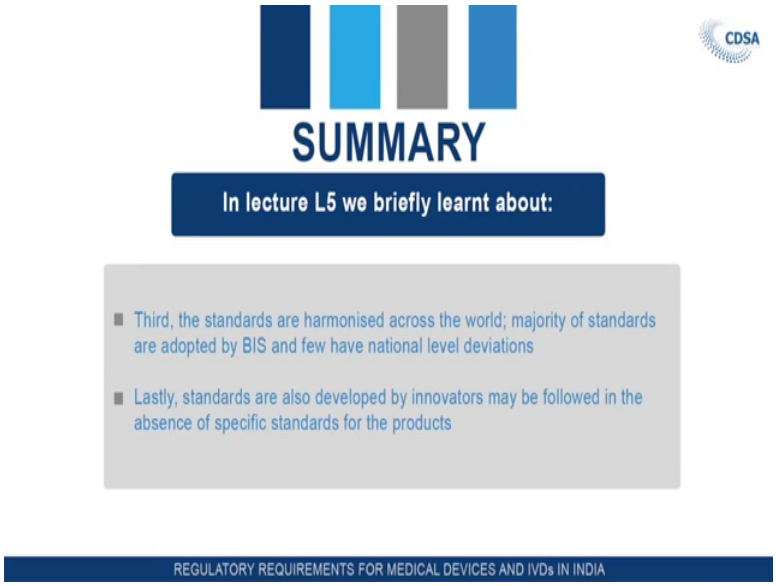

Third is standards are harmonised across the world majority of standards are adopted by BIS and few are have national level deviations. So, most of the standard that I have mentioned over here are appropriated by BIS also and it has become Indian standards. Lastly, standards are also developed by innovators 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 sterilisation and cleanroom to develop your own standards for the particular innovative standards innovative product and (Refer Time: 51:18) novel product.

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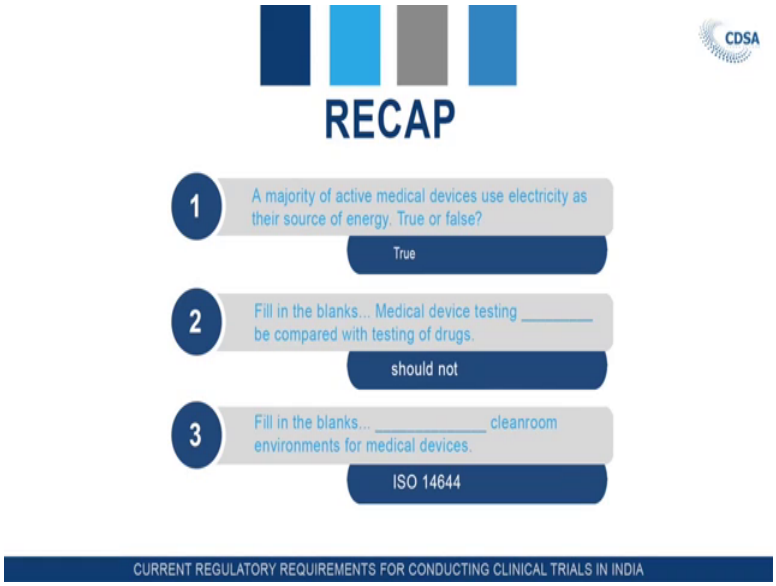

Now, some of the question and answers over the are over here very simple one; however, you will be getting much more question and answers you have to submit later on for assessment. So, that is over all.

Thank you very much.