Chapter 2
General Considerations for the Development of Biomedical Devices

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Abstract The development process of medical devices and of any products oriented to interacting with biological systems (biodevices) involves several special features deriving from the typical multidisciplinary characteristics of such devices and of their surrounding environment.

Therefore, the systematic development methodologies previously described have to integrate several additional special considerations and indeed very specific recommendations, for adequately helping to face up with the development of novel biodevices.

Aspects such as the existence of a relevant medical need; the effects of biological conditions; the selection of adequate biomaterials, sometimes with unusual mechanical and chemical properties; the consequences of corrosion; or the sterilisation methods available have to be considered, almost from the beginning, when developing a new biodevice. Development teams also integrate normally engineers, physicians, biologists and personnel from different disciplines, and sometimes, communication problems, together with project delays and even cost mismatches, arise. All this has to be taken into account in these projects.

The regulatory framework is also especially noteworthy in the medical device field, due to their potential harm when interacting with tissues and organs, and different directives have to be followed carefully. The most relevant EU directives of application for medical devices, together with advices included in important ISO standards, as well as some discussion and comparison with approaches from other countries (United States' FDA, Asian market…), are commented at the end of the chapter.

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A.D. Lantada (ed.), *Handbook on Advanced Design and Manufacturing Technologies for Biomedical Devices*, DOI 10.1007/978-1-4614-6789-2_2,

2.1 Basic Concepts Linked to Medical Devices or Products and Biodevices

A definition of medical device according to Council Directive 93/42/EEC of 14 June 1993 is "Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease.
- Diagnosis, monitoring, treatment, alleviation or compensation for any injury or handicap.
- Investigation, replacement or modification of the anatomy or of a physiological process.
- Control of conception, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means".

According to the US Food and Drug Administration, "A medical device is an instrument, apparatus, device, machine, appliance, implant, in vitro agent or other similar or related article, including a component part, or accessory which is:

- Recognized in the official "National Formulary" or the "United States Pharmacopoeia", or any supplement to them.
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease, in man or other animals.
- Intended to affect the structure or any function of the body of man or other animals and which does not achieve any of its primary purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes".

The first devices to come to light that fit these definitions date back to the Ancient Age. Evidence has been found in Ancient Egypt of various surgical instruments for performing trepanations and other surgical operations, as well as instruments intended for use in mummification and splints made of bamboo, cane, wood or the bark of trees. These would most surely have also been used to treat broken bones in living patients. An engraving made around the year 2800 B.C. at the entrance to the tomb of Hirkouf bears witness to the oldest use of a crutch.

Many of the principles referring to different conditions and their treatment are attributed to the Ancient Greeks (Laín Entralgo 1973). They may be considered the first to use a scientific methodology and were also the first to describe their history and progress in detail. Homer himself in his epic on the Trojan Wars reveals knowledge of the lesions of that period and the treatments used.

Between 430 and 330 B.C., a vitally important Greek text was compiled known as the "Corpus Hipocraticum". It was named after Hippocrates, who was called the

father of medicine. Hippocrates was born on the Island of Cos around the year 460 B.C. and died at a ripe old age in 370 B.C. He is known for having endowed medicine with a scientific, systematic methodology and for having defined for the first time the position and role of the doctor in society. Hippocrates possessed a thorough knowledge of fractures. He knew the principles of traction and counter-traction and developed special splints for tibia fractures similar to an external brace. He also designed the Hippocratic bench or "scamnum" to provide a support when realigning fractured bones.

Although many centuries have passed, the Hippocratic Oath continues to occupy a prominent position in medical practice.

Subsequently, Herofilus came to the fore in Alexandria in the third century BC for his study of the human body by dissecting corpses, which up to now had been considered sacred with anatomical studies only being performed on animals. There is clear proof that during the third to first centuries BC in Alexandria, postmortems were performed for the first time for investigative and diagnostic purposes and for which very advanced instruments were required.

During the second century BC of the Roman Empire, the most important figure of the period was Galen who stood out for his observation of medical phenomena and his attempts to find an answer. He carried out post mortems on dead gladiators in the coliseum at Pergamon. When this empire fell, all scientific progress came to a halt leaving only copyist monks in monastery libraries to act as the transmitters of ancient culture.

Then came the rise and development of Arab culture with its contributions to medicine and surgery. Avicenna (980–1037) stood out for his use of cauterisation by means of a hot iron, an instrument used to destroy organic tissue by the use of heat and also to stop bleeding. With the onset of the Renaissance, medicine and surgery was again given an impulse with the appearance of illustrated treatises on anatomy like the one by Vesalius (1514–1564). These advances continued throughout the following centuries with the ensuing improvements in surgical techniques as well as methods of anaesthesia.

However, the main advances in medical devices that came about throughout the 19th and 20th centuries were unfortunately as a result of the Great Wars. One example that speaks for itself is that in London alone in the Second World War, it has been calculated that over 260,000 l of blood were donated.

It is the direct responsibility of those of us who devote our lives to the progress of science and technology to make this situation change so that in the future such progress will never again be linked to a country's military might or be driven by the need to find a response to the effects of war but instead will be devoted to improving the life quality of human beings as its main objective.

At present, the world market for medical devices is estimated to stand at over 200 billion Euros and shows an annual growth of around 8 % (growth only surpassed by the pharmaceutical sector).

The European Union, as a whole, is the second producer with a market share of 30 %, with Spain as the fifth producer in the European Union with an EU market share of around 6 % (Pammolli et al. 2005). Different factors and technological

advances in recent decades have boosted the enormous growth of this highly economically important industrial sector, whose social impact is equally important. Set out below are the main factors that must drive study in this field and the never-ending search for solutions, as well as the main advances that have led to the rapid industrial expansion of this sector in recent years.

Socioeconomic Factors

- The considerable increase in life expectancy in the developed countries has led to a notable increase in the demand for implants, prostheses and orthopaedic devices as the number of patients with degenerative diseases has also increased. According to United Nations demographers, in around 5 years, there will probably be more people over 60 than children under 15.
- Nowadays, one out of every ten people is 60 or over, but in 2050, it is predicted that these figures will reach one in five, and the number of persons over the age of 80 will multiply five times. Greater longevity must go hand-in-hand with preserving the life quality of this group.
- The rising birth rate in underdeveloped countries together with the difficulty of access to basic needs favours the appearance of epidemics but whose treatment can be improved by the use of new devices for the controlled delivery of drugs, the use of disposable surgical instruments, birth control devices and other recent or predicted future developments of this industrial sector.

Recent Technological Advances

- Improvements to purchasing systems, processing, analysis and telecommunication of physiological signs, which have enabled patients to be more precisely monitored, both in the short term (e.g. during surgical operations and post-ops) and in the long term (studying the evolution of pathologies), by also enabling biological systems to be modelled and contribute physiopathological significance to the parameters found from processing (Deutsch et al. 2007, 2008; Cerutti 2008).
- The development of systems that interact between computers and the nervous systems of living beings based on two-way implants for receiving electric signals from the body and supplying current directly to the nervous system, which will open up new horizons for the treatment of neurological disease (Gasson et al. 2005; Warwick 2008).
- New micro-manufacturing and nano-manufacturing techniques, some based on the manufacturing techniques of integrated circuits but applicable to many more materials and shapes, have led to enormous reductions in the end-size of implantable devices with the additional possibility of fitting them with micro-instrumentation to endow them with “intelligence” (Gad-el-Hak 2003; Schwartz 2006).
- Optimising the product design process thanks to a combination of CAD-CAE-CAM and rapid prototyping which speed up the production start-up of devices by reducing intermediate stages and minimising costs (Kuklick 2006).

- The development of new bioabsorbable materials that are body compatible which degrade a certain time after being implanted while only producing non-toxic matter that can be eliminated or metabolised by the body. Outstanding progress has been made in the synthesis of bioabsorbable and biodegradable polymers that can be applied to a large number of devices designed for the controlled delivery of drugs (Lendlein and Langer 2002), as well as for support tasks for tissue engineering (Freed et al. 1994; Kawanishi et al. 2004).
- The discovery of new active materials that enable functionalities to be inbuilt and so open up new horizons for the development of active implantable medical devices thanks to their potential use as sensors and actuators (Davis 2003; Lendlein and Kelch 2005; Wong and Bronzino 2007; Peterson and Bronzino 2008).

These advances mutually favour one another and used in combination can provide multiple novel responses to conditions for which, up to a decade ago, there was no adequate treatment. All this has boosted the development of prototypes for a large number of medical devices, many of which benefit from the use of active materials.

The following section provides an introduction to the systematic process of product development and goes on to examine the further considerations that must be borne in mind should the device under development respond to a medical need. It will then go on to examine the influence of these considerations on the different stages of the proposed systematic process.

2.2 Special Issues for the Development of Biodevices

2.2.1 Special Difficulties

The design process of medical devices has a series of added difficulties that involve considerable changes and additional issues regarding the systematic methodology for designing the products previously mentioned.

These additional challenges, difficulties or issues can be classified into the three different groups set out below:

- Technical issues – These are related to the geometries, materials and the principles of functionality that can be utilised in a specific device as they are bounded by the implications involved by their contact with human body tissue. They are also bounded by the influence of the corporeal environment on the in-service performance of the materials used and their progressive deterioration due to this environment.
- Legal issues – The direct action on the body of the developed devices and their associated risks increase the responsibility of those involved in the design and give rise to certain changes to the prescribed methodology. The design process of medical devices is therefore subject to strict rules, and care must be taken to

adhere to the specific standards if end product safety is to be maximised. The official approval process for these devices also adds to the overall complexity of their development.

- Human issues – These are linked to the particular complexity of the design process for these products which require multidisciplinary teams with experts from the different branches of science, particularly, medicine, engineering, biology, chemistry and physics, among others, but which can lead to specific communication or coordination problems. On the other hand, it is important to point out that developing a new device should emerge as a result of a real human need, a factor that will be examined more closely further on.

The main additional issues to be taken into account when setting out to develop a new medical device are explained in the following subsections. Reference will also be made to the systematic methodology design stages explained previously, together with reflections on how the different issues influence these stages.

2.2.2 The Importance of a Relevant Medical Need

New developments and innovations in medicine and especially in the field of medical device design usually stem from a problem-related need, and then, a technological solution is found to solve the problem and satisfy the need (Kuklick 2006).

It is true that on some occasions a new technology or material can bring novel diagnostic or therapeutic solutions to concrete problems, but these technologically motivated products (instead of medically) only have an economic or social impact on rare occasions.

Thus, most companies and technology centres given over to the design of medical devices, as well as more effective devices, are based on the application of efficient technologies for resolving very specific clinical or surgical needs. The approach of studying new technologies and examining any possible applications by searching out medical needs is more linked to scientific research projects than with product development, which means that the results are not materialised in the form of commercial products.

However, both approaches have their own advantages and are perfectly valid depending on what the objective is. So, when designing a product, it is usually more effective to start out from a need and look for a technology to solve the problem. Although, if it is wished to promote scientific progress the option of developing a new technology and attempting to apply it to solve the needs of many varied sectors probably makes more sense.

Therefore, this handbook looks to both approaches. It shows the development of medical devices based on the use of novel technologies and materials, whose study and subsequent development is motivated by real medical needs requiring a technological solution.

On the other hand, throughout these development processes scientific and technological contributions are made concerning the use of design and manufacturing technologies for different conceptual trials linked to innovative developments, novelties that may find a use in future medical applications or even other sectors.

Regarding the development of new medical devices, it is important to emphasise that the need to provide a solution to a medical problem must be kept in mind at the very first "defining objectives and planning" stage. If no such need exists, it is hardly sensible to begin to develop a new product to provide a solution to a problem that does not exist or that is being satisfactorily solved by other means.

One particular skill of entrepreneurs or researchers in the field of medical devices is therefore the ability to search out and understand important clinical or surgical needs. It is a complex issue where it is not enough to carry out questionnaire-based market studies or an analysis of existing products to find gaps in the market. Often, there is no other product for comparison, particularly if the product to be developed is completely new.

All of this, in conjunction with the basic aims to ensure, lengthen and improve patients' quality of life, while at the same time generating economic and social value, complicates decision-making and the search for needs on which to work. Therefore, defining objectives for the development of medical devices is a particularly complex issue.

2.2.3 Biomaterials

As with the concept of medical device, there are various satisfactory definitions for the notion of "biomaterial". The term generally designates any material used in the manufacture of devices that interact with biological systems and that are applied in the different branches of medicine (Wong and Bronzino 2007; Peterson and Bronzino 2008). This definition includes materials with very different properties and classifiable into different families, such as metals, ceramics, polymers and composite materials. According to their origin they can also be classified as natural or synthetic. Another possible classification is based on the influence the biomaterial has on the body or the extent of the reaction it produces on surrounding tissues, the following division being generally accepted:

- Bio-inert materials – Characterised by their low reactivity in the body, which means they can coexist with the surrounding tissue without any apparent change to the functions and properties of this tissue. Typical materials of this kind used in implantable devices are tantalum, titanium, aluminium, magnesium and some zirconium oxides.
- Biodegradable or bioabsorbable materials – They have the capability to be body compatible and to degrade a certain time after implant, giving rise to non-toxic products that can be eliminated or metabolised by the body. Some materials of

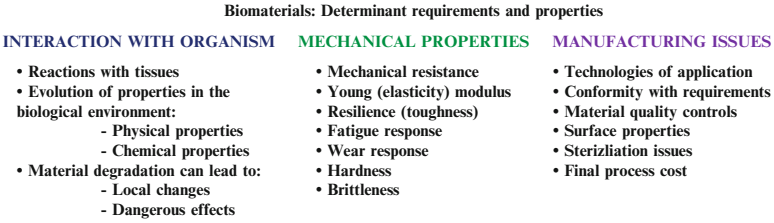

Fig. 2.1 Properties and determining factors for choosing biomaterials

this family are porous hydroxyapatite, the salts of calcium phosphate and some polyurethanes.

- Bioactive materials – They have the ability to form direct chemical ties with the surrounding tissue allowing this tissue to grow freely on their surface. Some examples of these materials are high density hydroxyapatite and tricalcic phosphate.

All materials used in medical device development, particularly those that will be in contact with body tissues, must meet a set of manufacturing and chemical requirements and properties and body-compatibility requirements, which are mainly mechanical. These are listed in Fig. 2.1 and Table 2.1 shows typical examples of synthetic materials applied to obtain medical devices.

2.2.4 Body Conditions

When it comes to choosing suitable materials for a product under development, during the basic engineering stage it is usually essential to consider the environment in which the product is going to act. The particular case of medical devices is no exception and body conditions play a deciding role when choosing materials.

Conditions such as a temperature of around 37 °C are not extreme for the materials used in medical devices. However, if active material-based devices are used whose activation is based on a change in temperature, the limits admitted by the body must be taken into account, as will be commented later.

Although temperatures are not usually a big problem, the biomechanical demands and chemical circumstances of the body are usually decisive when choosing the appropriate material for a medical device.

Regarding the mechanical demands, it is essential to bear in mind not only the nominal value of the demand but also the complete load cycle and the number of load cycles to be supported by the device. A typical hip prosthesis may be subjected to $3 \cdot 10^6$ load cycles per year, which in the case of a person of 25, with a 70-year life expectancy, would mean around 108 load cycles in the most unfavourable scenario. Although loads and load cycles depend directly on weight and each specific patient's

Table 2.1 Examples of materials in medical applications

Material	Main applications
Metals and alloys	
Stainless steels	Clamping fractures, stents and surgical instruments
Co-Ti, Ti-Al-V, Ti-Al-Nb, Ti-13Nb-13Zr, Ti-Mo-Zr-Fe	Bone and joint prostheses, clamping fractures, dental implants
Co-Cr-Mo, Cr-Ni-Cr-Mo	Bone prostheses, clamping fractures, dental implants, heart valves
Ni-Ti	Self-expanding stents, bone plates, clamping fractures, orthodoncy wires
NiTi, NiNbTi	Coating for biocompatible implants
Gold alloys	Dental repairs
Silver products	Antibacterial agents
Platinum and Pt-Ir	Electrodes
Amalgam of Hg-Ag-Sn	Dental repairs
Ceramics	
Aluminium	Joint prostheses, dental repairs
Zirconium	Joint prostheses
Calcium phosphates	Bone repairs, metal and alloy surface coatings
Glass	Bone prostheses
Porcelain	Dental repairs
Carbon coatings	Heart valves, percutaneous devices, dental implants
Polymers	
Polyethylene UHMWPE	Joint prostheses
Polypropylene	Sutures
PET	Sutures and vascular prostheses
Polyamides	Sutures
PTFE	Vascular prostheses and in vitro tissue growth
Polyesters	Vascular prostheses and drug delivery devices
Polyurethanes	Devices in contact with blood
PVC	Conducts for pumping operations, drug delivery and others
PMMA	Contact lenses
Silicones	Implants and soft tissue replacement
Hydrogels	Ophthalmology and drug delivery
PVA, PCL, PLGA…	Scaffolds for tissue engineering
Composites	
Bis-GMA – quartz	Dental repairs
PMMA – glass filling	Dental repairs and bone cements

level of activity, it is patently obvious that the effects of mechanical fatigue in the response of the materials used need to be taken into account.

On the other hand, any variation in the chemical state of the environment is decisive when choosing a particular material for a device. In this respect, any changes in the pH of the body fluids must be carefully examined.

Blood pH usually remains between 7.38 and 7.41. However, after an operation the pH may increase locally up to 7.8 and then decrease to around 5.5, returning to its normal value after a few weeks.

Infections or haematomas can also give rise to local variations in the pH and situate it between values of 4 and 9.

These variations are important when choosing material (and its processing) for a metal prosthesis where a proper resistance to corrosion must be ensured.

Likewise, the pH of saliva, usually between 5 and 7, is a determining factor when choosing materials for implants or dental repairs.

According to the issues considered up to now, we will summarise the most important requirements to be met by a medical device and the materials of which it is made:

- It must not be toxic or carcinogenic, cause a minimum adverse reaction and be chemically stable and corrosion resistant, as will be explained in detail further on in connection with biocompatibility.
- It must be capable of withstanding considerable forces and variables inside the human body, that is to say, in a highly corrosive environment.
- It must be capable of being shaped into complex forms in order to adapt to the geometrical requisites of the body.

From an economic point of view, it is also desirable for biomaterials as well as their manufacturing and transformation processes to be relatively low cost with a high market availability to avoid dead time during the development process.

Explained below are some of these requirements in relation to the functions that medical devices usually need to perform. Also analysed is the influence of the body on that performance.

2.2.5 Biocompatibility

Like other important scientific concepts that evolve over time, the definition of biocompatibility has gradually changed with the advances made in materials intended for medical devices. Until a few years ago, a biocompatible material was one that did not harm the body. They were basically inert materials "possessing the property of not causing any harm or toxic affects to biological systems".

However, new developments, including those that are active material-based, have made this definition change to "the capability of a material to properly fulfil its mission in a specific application for a particular patient". The concept thus presents four basic aspects:

- Biocompatibility makes no reference to an isolated event or phenomenon. It applies to a set of processes that include diverse mechanisms for an interaction between the material and the surrounding biological tissue.

- Biocompatibility refers to a material's capability to perform a function in the body and not simply to remain inert in the body. Moreover, the material's capability to carry out its function not only depends on the physical–chemical properties inherent to the material but also on its interaction with tissue.
- It is important to take account of the positive response on the part of the particular patient or host of the device. A lack of response is no longer sought, but that the response, however slight, should be in accordance with the device's function.
- The most up-to-date definition also makes reference to the specific application. For example, the same material with different geometries or in different organs, in one case can be a final biocompatible application, whereas in the other situation it may fail.

Biocompatibility cannot therefore be considered an intrinsic material property, but must be approached from a more global perspective that involves the whole set, material–application–body.

A good starting point for looking at biocompatibility throughout the different medical device development stages can be found by consulting ISO Standard 10993 on the "biological evaluation of medical devices". It describes a guided process for choosing the tests required to evaluate a device's biocompatibility depending on its degree of contact with body tissue and risks associated with its use. It also includes various procedures for performing specific tests.

In principle, right from the basic engineering stage, it is reasonable to choose materials that have given positive results in other applications, but throughout the detailed engineering stage the material chosen for the new application needs to be checked in every case to ensure that it meets biocompatibility requirements by carrying out the tests (both in vitro and in vivo tests) described in the Standard.

2.2.6 Mechanical Behaviour

Metal materials are used in implants and prostheses for their remarkable mechanical properties and particularly for their high static and dynamic strength. The main properties to consider when choosing a metal material to withstand mechanical forces are flow tension, tensile strength, elasticity modulus and fatigue resistance. These can be known from the information provided by the suppliers or be obtained through the appropriate tests.

Ceramic materials offer an excellent resistance to compression, for which reason they are used in numerous applications in Odontology. However, their performance in the face of flexion and fatigue is insufficient because the forces appearing cause the cracks to appear and propagate, which leads to a fragile rupture of these materials.

Among the properties to be considered when choosing polymeric materials that are to be subject to forces as part of implants or prostheses is that they should have a remarkable tensile strength, flow tension and fatigue resistance.

Moreover, with polymers the influence of working temperature on these properties must be taken into account when consulting supplier information or carrying out tests to determine such information.

Set out below are certain general issues related to the mechanical aspects that influence the response of different materials in their useful life as component parts of medical devices.

Test-related issues – In ideal conditions the tests for determining mechanical properties should be performed in an environment identical to the human body where the device is going to work. In practice, due to technical and financial difficulties and timelines, they are normally carried out at ambient temperature and in contact with the air. However, when assessing any possible degradations, tests can be performed in fluids that simulate body properties (isotonic solutions with blood and others).

Fatigue-related issues – Implants and prostheses receive cyclical loads during body movement that promote the appearance of cracks in zones where the tensions are usually concentrated due to irregularities in the microstructure of the material because of surface finish defects or inappropriate design. Influencing factors on this phenomenon such as shape, material, manufacturing process, surface finish and others make it difficult to measure the fatigue resistance of a specific part in the design stage, which is why test results have to be resorted to.

However, testing implants under real load and contour conditions that simulate actual implant performance inside the body is also a very complex and expensive task. Therefore, standardised tests are normally performed with a sample of the candidate materials or the information provided by the suppliers. To assess behaviour in the face of fatigue, the tests described in the documents prepared by the ISO TC164/SC5 committee or those explained in US standards like ASTM F1160, F1440, F1539, F1659, F1717 and F1798 can be used.

Wear-related issues – Resistance to wear is also a decisive criterion when choosing a biomaterial as excess wear cam leads to the premature failure of an implant or prosthesis. It is also important to point out that the residue from the wear must be body compatible in order to prevent the appearance of infection or long-term rejection. Information on this can be found in ISO Standard 10993 (Parts 13–15) which suggests criteria for assessing body compatibility and wear residue.

Other test methods for assessing the performance of different implant materials and different geometries can be found in the documents prepared by the ISO TC150/SC4 committee or in US standards like ASTM F732, F1714 and F1715.

For example, wear in contact between polymers like UHMWPE and metal alloys or ceramic materials has been studied for over 40 years. In general, research into material wear for prostheses goes along one of the following three lines:

- The use of test machines to do basic research into wear mechanisms by using samples of different materials

- Assessing complete prosthetic mechanisms during the in vitro test period when they are subjected to static or dynamic loads using simulators
- Analysing the in vivo evolution of prostheses implanted in patients using medical imaging technology

Elasticity-related issues – As already explained, the need for high static and dynamic strength has led to the extended use of metals and alloys for designing prostheses and implants, particularly cobalt alloys and titanium alloys. However, there are still a number of unsolved problems associated with the use of these alloys, some due to their stiffness being higher than the bones in which they are housed.

Numerous studies show that the bone areas surrounding an implant that receive less load suffer loss of bone mass and therefore mechanical strength (osteoporosis), a phenomenon attributed to the difference in stiffness between implants and the bones in which they are housed, which leads to unequal distributions of forces in the implant-bone contact zone.

Proposals for more flexible solutions to encourage the prosthesis to accompany the bone in its movements and obtain force distributions more like those in a healthy body have led to materials with lower elasticity moduli to be sought and developed.

Composite materials with a polymeric matrix are currently being tested as candidates to replace cobalt or titanium alloys, although problems of degradation and tribological difficulties are hindering it in vivo application.

The mechanical issues set out affect different stages of the previously mentioned systematic design methodology. In principle, in the basic engineering design stage the mechanical demands to which the device will be subjected should be precisely defined.

The family of materials most suited to bearing these loads should also be selected. In the detailed engineering stage, the main candidate materials are compared and the final material is chosen.

2.2.7 Corrosion and Deterioration

We have already introduced the problems linked to the body as a corrosive environment and how this has an influence on the final compatibility of devices, as well as being a determining factor for choosing materials during the basic engineering stage.

Some additional issues are examined below that depend on the material family that is to be integrated into the specific device.

Corrosion in metals – The metals used as biomaterials must be noble and resistant to their surroundings (body fluids). Various types of corrosion mechanisms have been observed in the metal materials forming part of implantable devices – general corrosion local corrosion or “pitting”, corrosion due to a concentration of tensions, corrosion due to fatigue and intergranular corrosion.

In whichever case, for a material to be considered resistant to bodily effects, the annual corrosion rate must be lower than $25 \cdot 10^{-6}$ mm/year. A series of standard tests have been developed for assessing behaviour of implant materials in the face of corrosion, such as those set out in ISO Standard 8044 prepared by the ISO TC156 expert committee or those set out in US standards such as ASTM F746, F897, F1801, F1814 and F1875. For assessing the behaviour of coatings in the face of corrosion, the tests described in the ISO TC107/SC7 documents can be followed.

Corrosion in ceramics – Corrosion tests for ceramic materials are not habitual as the ceramic oxides normally used in structural implants are very few. However, some ceramics do show certain in vivo corrosion which affects their mechanical behaviour.

For this reason, in the detailed engineering stage a very exact definition of the manufacturing processes and the transformations required for these materials is very important, as well as specifying the required purity and density (in general, the greater the density the less the porosity and the greater the resistance to corrosion).

Corrosion in polymers – Although the physiological functions and chemical reactions taking place in the body do not occur at high temperatures or with radioactive effects, combining an electrolyte with active biological species, like catalytic enzymes and free radicals, constitutes a particularly reactive environment which leads to a certain degradation of numerous polymers.

Of the individual mechanisms linked to polymer degradation in the body (Davis 2003), there are:

- Depolymerisation
- Cross-linking
- Oxidation
- Adhesive filtering
- Hydrolysis
- Crack generation and propagation
- Physical ageing

These mechanisms and their possible effects on the final product must be borne in mind at the basic engineering stage when choosing the most suitable materials for body circumstances as well as for making decisions as to the use of additives that can restrict these problems. The geometries and ways of joining parts can also have an influence on the appearance of these phenomena.

It is therefore important to take notice of the recommendations in the manufacturers' design manuals and technical catalogues for the final material to be chosen in the detailed engineering stage.

Test procedures for evaluating the effects of residue resulting from the corrosion and degradation of polymeric, ceramic and metal materials (and their influence on the biocompatibility of the final materials) can be found in ISO Standard 10993, parts 13, 14 and 15, respectively.

2.2.8 Sterilisation

Sterilisation is also essential for all implanted materials and devices. In medical practice, financial considerations often lead to surgical instruments and costly equipment being used over and over, which means they need to be sterilised after each use with a new patient.

Every sterilisation method must pursue the same objective: to eliminate or destroy living organisms and viruses present in the biomaterial or the medical device to be implanted. This process is usually quantified by the so-called SAL or sterility assurance limit.

The details of the sterilisation method are determined from tests until the SAL obtained (the probability that an implant will not be sterile after the process) is less than 10^{-6}.

The principal sterilisation methods (Davis 2003, Simmons 2004; Kuklick 2006) are explained below:

Steam sterilisation – Steam or autoclave sterilisation is a simple method based on exposing the device to saturated steam at 120 °C for 15–30 min (once the entire implant surface has reached 120 °C) at a standard pressure of 121 kPa. This is the most widely used method for sterilising metal surgical instruments. The method's main advantages are its effectiveness, rapidity, simplicity and lack of toxic residue. However, the high temperature, humidity and pressure during this type of sterilisation cause the hydrolysis, softening and degradation of many medical grade polymers and problems with any adhesives that may have been used.

Ethylene oxide sterilisation – This is used as a low temperature process that is compatible with many materials. The device is placed in a vacuum chamber into which ethylene oxide is injected at a concentration of 600–1,200 mg/l. The steriliser is usually kept at a temperature of between 30 °C and 50 °C and 40–90 % relative humidity during the process which lasts from 2 to 48 h. It is usually used for sterilising a wide range of devices such as surgical sutures, intraocular lenses and devices for repairing ligaments and tendons or heart valves.

The main disadvantage is that ethylene oxide is toxic and possibly carcinogenic, and so, its use in implantable devices is controversial. Eye contact or inhalation of the vapours resulting from the process should always be avoided.

Sterilisation by radiation – Ionising gamma ray radiation from cobalt-60 isotopes is used in dosages ranging from 25 to 40 kGy. The dosage is controlled by a dose meter to ensure the integrity of the device so that it will not be radioactive after the process and can be used immediately.

This is an appropriate process when materials cannot withstand the high autoclave temperatures. It is widely used for sterilising sutures, clips, metal implants, knee and hip prostheses and other implants. It has also been commonly accepted as the most suitable way of sterilising polymeric materials such as polyethylene, polyesters, polystyrenes, polysulphones and polycarbonates. Some exceptions are polytetrafluoroethylene ("PTFE" commonly known as Teflon) because of its extreme sensitivity to radiation.

It is a simple, fast method that can be precisely controlled, but it is not without certain difficulties. In some cases the method can produce a certain oxidation of the polymers sterilised by this method, as has been recorded in some "UHMWPE" implants. This usually leads to an increase in density and crystallinity, as well as a loss of the mechanical properties linked to the greater stiffness acquired.

However, this problem can be considerably reduced by carrying out the process in an inert gas atmosphere (argon, nitrogen) or in a vacuum chamber to reduce the presence of oxidising species and enhance the properties and useful life of "UHMWPE" devices.

New sterilisation techniques – Sterilisation in low temperature plasma is one method that has given positive results over the last decade, since it is not linked to the use of dangerous products and does not generate toxic waste. Hydrogen peroxide is usually used as the gas to form the plasma and the process is carried out at temperatures below 50 °C with cycle times of between 75 min and 3 h.

Ionised gases such as argon, nitrogen, oxygen and carbon dioxide have also been used to destroy surface microorganisms with low processing times of between 15 and 30 min.

The process has been used to sterilise polymers like polylactic acid ("PLA"), polyglycolic acid ("PGA") and its copolymers ("PLGA").

Carbon dioxide in a supercritical state has also been used to inactivate bacteria in applications including biodegradable polymers such as "PLA" and "PLGA" for drug delivery systems as well as prostheses made of polyester fabric.

So, sterilisation is usually an after-sales activity that is applied to a developed product. However, it also has an influence on the design process since as a prior step to in vivo tests in the detailed engineering stage, the device under development must also be subjected to sterilisation with the purpose of minimising any risks associated with these in vivo tests.

2.2.9 Multidisciplinary Teams

Product design projects connected with developing a new medical device are probably the ones requiring a team trained by experts from a number of fields, especially if the device incorporates means of detection or can be activated for the diagnosis or active treatment of some condition. A standard design team for these devices is usually made up of doctors, pharmacologists, engineers, computer experts, physicists, chemists and biologists in addition to economics and law graduates to deal with the financial and legal aspects. The design process obviously benefits from such a wealth of approaches and at the same time is a highly attractive working environment. However, the availability of experts in specific fields can also give rise to problems of communication (misunderstandings, lack of precision, lack of information, false suppositions) that can cause the timescales and costs of specific work to go off course and even lead to personal conflicts that affect the project as a whole.

We need to be aware that working in a global context is ever more usual and that the participation of designers, suppliers and customers from different countries who have a decisive influence on the design process means an increase in communication problems. It is worthwhile making yet another effort to improve understanding as the wide-ranging points of view of multinational teams can be a tremendous help in finding more consistent solutions. Some strategies for using a common language throughout the design process will be discussed further on (use of documents to define the initial situation, a general use of the International Units System, the participation of experts or communication "facility advisors"), together with certain teaching-related considerations and proposals, a key tool for providing a short-term response to the potential growth of this sector.

2.2.10 Regulations

The intrinsically complex process of product development linked to the additional problems already mentioned connected with medical devices means that consulting the recommendations regarding regulatory standards for the different design stages often marks the difference between a successful design process and an unviable one.

The concept of regulatory standards is closely linked to end medical device quality and safety, for which reason it deserves to be dealt with separately in the next sub-chapter.

2.3 Discussion on Applicable Standards

2.3.1 Standards in Conventional Product Development

As stated earlier on, quality and safety are interlinked and together with productivity constitute the basic issues to be taken into consideration in product design and mark all the difference between successful strategies and ones that are not.

Indeed, the trade promotion sought by the European Union through the internal market required additional safety issues for the products commercialised in that market, so that such promotion would not have any negative consequences on the products marketed, particularly industrial products.

This led to a common community policy being adopted based on the "new approach directives", whose application has enabled an homogenised framework of technical references to be established that are valid for all community countries and which hold sway over specific domestic requirements which cannot prevail over the framework. This means an abolition of technical barriers which is coherent with the disappearance of customs barriers.

Therefore, the new approach directives for different product types or sectors set out the basic safety and quality requirements to be met by these products, as well as the checks and tests that must be passed (before duly recognised bodies), before receiving the "CE mark" and being able to be marketed in the European Union.

In order to give "this new approach" solid foundations, the European Union and, in particular, the Commission have used quality techniques applied to the context of product conformity in respect of the applicable European requirements, basing them specifically on the triad of standardisation–certification–accreditation, in order to endow the tests and checks with guidelines and patterns that can be commonly accepted.

Given that standards and quality have come to occupy an important position in the community marketing policy for industrial products, it is not surprising that this official European initiative should end up becoming part of the most widely accepted international standards in the field of quality, to be exact ISO Series 9000 standards.

It is important to distinguish between directive and standard since the new approach directives are mandatory for placing products on the market in the European Union (obtaining the CE mark), while the standards of organisations like the ISO are proposals or recommendations for working more methodically and effectively.

However, the use of ISO Series 9000 quality standards is recognised by many of the new approach directives as a means of showing conformity with the requirements of these directives and specifically to allow the use of the CE mark.

On the other hand, conformity with the 45000 Series European standards provides organisations with "conformity assessment", the presumption of conformity with the technical criteria set out in the directives.

Thus, the use of 9,000 Series or 45,000 Series standards is not one of the mandatory requirements of the new approach legislation but is one possible way of demonstrating conformity.

The directives that apply to the design of medical devices in the European Union are explained further on in greater detail.

2.3.2 Regulations and the Development of Medical Devices

Directives. Regarding the development of medical devices in the European Union, there are three directives (with their associated amendments) which must be taken into account in order to be able to market the products under development:

- Directive 93/42/EEC regarding medical devices
- Directive 90/385/EEC regarding active implantable medical devices
- Directive 98/79/EC regarding medical devices for in vitro diagnosis

2.3.2.1 Directive 93/42/EEC Regarding Medical Devices

This directive applies to medical devices and accessories where a "medical device" comes under the definition cited at the beginning of the chapter, which can be summarised as "any instrument, apparatus, tool, material or other article, either used on its own or in combination with others, including the operating system required for it to be properly applied in the way intended by the manufacturer for use in human beings".

A "medical accessory" is an article, which, although it is not a device, has been manufactured to be used together with a device in such a way that its use is compatible with the use of the device as intended by the manufacturer.

Medical devices are classified under two headings in line with the classification standards laid down in Annex IX of the directive. The application of these classification standards is governed by the device's intended purpose, the risks associated with its use, the extent of contact with body tissue or the time it will remain in the human body. Therefore, medical devices in order of danger/increasing responsibility may be "Class I", "Class II a", "Class II b" or "Class III".

Before manufacturing and placing the device on the market, the manufacturer or its authorised agent in the European Union must subject it to different types of controls depending on how it is classified if the device is to bear the CE mark.

These controls are listed below:

For "Class I" Devices

For sterilised devices and devices with a measuring function, the "CE declaration of conformity" must be obtained before placing them on the market and then at the manufacturer or agent's choice:

- The "CE verification" by a notified body
- Approval of the "production quality system" by a notified body
- Approval of the "product quality system" by a notified body

Other devices must pass the "internal production control", that is, all the technical documentation necessary for the product's declaration of conformity in line with the requirements of the directives must be prepared and submitted to evaluation.

For "Class II a" Devices

At the manufacturer or agent's choice, these products must obtain:

- The "EC declaration of conformity" and depending on the choice
  - The "EC verification" by a notified body
  - Approval of the "production quality system" by a notified body
  - Approval of the "product quality system" by a notified body

These alternative procedures are mandatory for sterilised devices.

- As an alternative the manufacturer must receive approval of the "total quality assurance system" by a notified body, with the exception of having to apply the product design examination.

For "Class II b" Devices

At the manufacturer or agent's choice, these products must obtain:

- The "EC type examination" and depending on the choice:
  - The "EC verification" by a notified body
  - Approval of the "production quality system" by a notified body
  - Approval of the "product quality system" by a notified body
- As an alternative the manufacturer must receive approval of the "total quality assurance system" by a notified body, with the exception of having to apply the product design examination.

For "Class III" Devices

At the manufacturer or agent's choice, these products must obtain:

- The "EC type examination" and depending on the choice:
  - The "EC verification" by a notified body
  - Approval of the "production quality system" by a notified body
  - Approval of the "product quality system" by a notified body
- As an alternative the manufacturer must receive approval by the "total quality assurance system" by a notified body, including having to apply the product design examination.

For devices intended for clinical research and custom-made devices, the manufacturer must prepare a declaration in accordance with the criteria in Annex VIII of the directive. These research-oriented devices should not to bear the CE conformity mark.

The directive does not identify any quality system standard, but the requirements provided to create the quality system are subject to ISO 9000 Series regarding the total quality system, the production quality system and the end product quality system. In order to evaluate the technical competence of the notified bodies, the member countries of the EU must implement the criteria laid down in Annex XI of the directive.

2.3.2.2 Directive 90/385/EEC Regarding Active Implantable Medical Devices

This directive applies to active implantable medical devices, that is to say, "any medical device (as defined previously) that depends on an electrical power supply to operate it (or any energy source not directly generated by the human body or by the force of gravity) and which must be totally or partially inserted into the human body by surgical or medical means, or into a natural orifice by medical intervention and remain permanently installed after the procedure".

Before placing the product on the market, the manufacturer must subject it to the procedures to evaluate conformity that are laid down in the directive. Except for custom-made medical devices and those intended for clinical research, the manufacturer may opt to:

- Follow the procedure laid down in the "CE declaration of conformity" (approval and verification of the total quality system by a notified body) supplemented by the product design examination
- Subject a model to the "EC type examination" by a notified body in conjunction with one of the following processes:
  - The "EC verification" for devices by a notified body
  - The "EC declaration of conformity"

For devices intended for clinical research and custom-made devices, the manufacturer must prepare a specific declaration. These devices do not have to bear the CE mark.

This directive does not identify any quality system standard either, but the requirements provided to create the quality system are subject to ISO 9000 Series standards regarding the total quality system, the production quality system and the end product quality system.

2.3.2.3 Directive 98/79/EC Regarding Medical Devices for In Vitro Diagnosis

This directive covers in vitro devices, whose mission is to examine the specimens and samples derived from the human body, reagents, instruments and specimen receptacles linked to these tests. Placing these devices on the market is once again subject to conformity with the directive. In greater detail, for the directive an in vitro diagnostic medical device is "any medical device including reagents, calibres, control material, instruments, apparatus, equipment or systems which used on their own or in combination are intended for in vitro use to examine specimens, including blood and tissue, derived from the human body in order to obtain information on: pathologies, congenital defects, safety and compatibility with potential receivers or therapeutic measurement monitoring".

This definition must be examined in conjunction with what has already been stated for a medical device; for instance, several scaffolds for tissue engineering can be considered implantable devices, devices for in vitro diagnosis or even active implantable devices, depending on their final purpose.

Although these devices do not act directly on the human body, the responsibility connected with their use is still very high as they can be used to supplement the design process of other implantable or active medical devices. In addition, their use in detecting conditions, congenital defects and for monitoring, directly affects the patient, which means the reliability and rapidity of these devices are determining factors.

For this reason, in vitro diagnostic devices are divided into four classes in order of risk and must be subject to different controls according to the operating instructions in the directive before being placed on the market. The alternatives that can be chosen by manufacturers are similar to what has already been stated regarding the previously mentioned directives and can be examined in more detail by referring to the directive.

Specific regulations – As we have already seen for conventional products, when developing medical devices and sanitary products, in general terms, following the recommendations on quality and procedures laid down in ISO 9000 Series standards, in conjunction with some specific features of ISO 13485 and 13488 standards, although not obligatory, is one way of demonstrating conformity with the requirements of the three specific directives and specifically allow the use of the CE mark.

However, there are certain standards and documents regarding very specific aspects of medical device development which are worth looking at and trying to implement, apart from the ISO 9000 Series, when developing a product from this sector intended for placement on the market, such as:

- ISO Standard 10993 on the "biological evaluation of medical devices".
- ISO Standard 13485 on "sanitary products, quality management systems and regulatory requirements" (replaces Standard EN 46001). It lays down the requirements for a quality management system where an organisation needs to demonstrate its ability to design, develop and supply related sanitary products and services that consistently fulfil the customer's needs and the regulations applicable to sanitary products and related services. The main objective of ISO 13485 is to facilitate harmonised regulatory requirements for quality management systems and sanitary products. Consequently, it includes some specific requirements for sanitary products and excludes some requirements of ISO Standard 9001.
- ISO Standard 13488 on "sanitary products, quality management systems and specific requirements for the implementation of ISO Standard 9002" (replaces Standard EN 46002). In conjunction with ISO Standard 9002, it specifies the quality requirements for a company producing, installing and distributing medical devices.
- ISO Standard 14971 on the "application of risk management to sanitary products". This indicates the process to be followed by designers in order to identify

the risks associated with medical devices including those intended for in vitro diagnosis, so that these risks can estimated and evaluated and attempted to be controlled by corrective actions and then verify the impact and effectiveness of such corrective actions. It can be applied to every step of the life cycle of the medical device in question.

- ISO Standard 15223 on the "symbols to be used with labels, labelling and information to be supplied with medical devices". This identifies the requirements for the design and use of any symbols that may be intended to provide safe, effective information about medical devices.

Together with these general standards referring to the area of medical devices, throughout the design process of these products, it can be extremely useful to refer to the specific regulations connected with the methods for characterising and testing the different materials so that objective comparisons can be made of any possible alternatives or be of help in choosing suppliers (depending on the regulations used to verify materials or products).

At the same time regulations are in a constant state of flux as they attempt to adapt to safety and market quality requirements and to cover the latest advances in science and technology that demand changes to product designs. It is therefore important to regularly check updated references (www.iso.org).

The situation in other countries – In general, in order to assess the biocompatibility of a medical device, the strategies complying with what is laid down in ISO Standard 10993 are acceptable usually both in Europe and in Asia (Kuklick 2006).

However, in the United States the test procedures of the US Pharmacopeia, used to subsequently request product certification from the FDA (Food and Drug Administration), have certain differences compared to ISO standards. Generally speaking, ISO procedures are stricter, which means that companies intending to market their products both in Europe and the United States must follow ISO requirements. Nevertheless, in both cases, after applying ISO methods and before placing products on the US market the requirements of the FDA must be carefully checked and if necessary additional testing be done. It may even be necessary to enlist the help of FDA reviewers to clarify matters.

Research and regulations – As we have seen from our examination of the new approach directives concerning medical devices, for products intended for clinical research and custom-made products, the manufacturer must prepare a declaration in line with the criteria of the appropriate directive.

However, it is not necessary to undergo such strict examinations as for products intended for the market. In fact, medical devices for research or custom-made ones do not have to bear the CE mark.

A certain relaxation as to the application of standards would seem reasonable in the case of research devices as they are often intended to demonstrate the feasibility of a certain functional principal, often as part of the design process of a product to be placed on the market in the long term. This additional freedom is aimed at encouraging a creative spirit rather than rejecting solutions and alternatives because

of regulatory difficulties. It encourages technical feasibility (and economic) studies concerning the use of novel materials or technologies.

Finally, it is important to mention the "Helsinki Declaration" enacted by the World Medical Association in 1964 with six subsequent amendments, the latest being in 2008 and currently in force. The declaration is a proposal of ethical principles for medical research in human beings, including the research of human material and identifiable information. It also deals with the ethical issues involved in vivo tests conducted on animals as a prior step to their being conducted on humans.

Although application of the Declaration is not mandatory for placing a new device on the market, it establishes a set of ethical principles that can guide and assist researchers to make decisions in medicine-related matters, as well as assisting those of us who are dedicated to "biomedical engineering" work. The purpose of these decisions is to ensure the well-being of any persons taking part in research, over and above any other considerations, and as a result more effective and safer products are obtained.

The principles of the Helsinki Declaration are also beginning to take on economic (as well as ethical) importance, compliance with which is a sine qua non of being awarded biomedical research projects in many countries. This can be seen in calls for the current National I + D + i Plan for the 2008–2011 period and constitutes a strategic point of Spanish policy in matters of research, development and industrial innovation, in a similar way to what happens in other European countries.

2.4 Main Conclusions

Various socio-economic factors are driving the growth of the medical device development industry, all aimed at providing alternative diagnostic and therapeutic and sometimes more effective solutions than those currently available. This growth will be based on recent scientific and technological progress. However, if this growth is to be given a solid foundation and the proportion of devices finally being placed on the market increased, it is important that systematic product design methodologies are used that have been duly adapted in line with the specific additional considerations required for the medical devices to be properly developed.

After studying the stages usually used in a systematic product design methodology and analysing how the main special considerations mentioned influence this methodology, we can evaluate which steps and considerations require deeper analysis as a result of their greater relative importance.

Table 2.2 quantifies the influence of different special considerations on medical devices in the systematic design process stages. It also includes the device's useful life due to the implications involved in post-production activities.

This table can also be used as a control tool throughout the design process to ensure that the special considerations of greatest influence at each stage have been taken into account before a stage is deemed to have been completed.

It should be pointed out that in medical device development projects, there are many additional factors that have a decisive impact on the useful life of these devices

Table 2.2 Influence of different factors on the development process of medical devices. Degree of influence: *average **high ***very high

	Medical device development					
Special considerations	Specifications and planning	Conceptual design	Basic engineering	Detailed engineering	Production start-up	Device's useful life
Medical need	***	**	**	*		***
Biomaterials	*	**	***	**	*	***
Body conditions	**	*	**	**		***
Biocompatibility	**	*	***	**	**	***
Corrosion	*	*	**	**	*	***
Mechanical performance	*	*	**	**	*	***
Sterilisation			*	*	*	***
Communication	***	**	**	***	**	*
Regulations	*	*	*	***	***	***
Quality	*	***	***	***	***	***

and which involve special difficulties. However, the use of systematic structured design methodologies, keeping to regulations, and a constant concern for quality and good communication within the design team can help lead to effective, safe end products.

Any projects arising out of clear medical needs (clinical, surgical, diagnostic or therapeutic) where initial requirements are accurately defined will have a far greater chance of success. The basic engineering stage is a particularly critical part of the design due to its being responsible for contributing specific solutions to the devices main functions. On the other hand, adhering to certain ethical standards and principles connected with the direct repercussions to be had on a person's health by using these devices can also be highly useful throughout the design process, particularly for making decisions or choosing alternatives that cannot simply be based on technical criteria alone.

The last thing to be examined should be any modifications or additions to the stages of the proposed methodology that will make it easier to implement new technologies or materials (especially "active or intelligent materials" and "new biomaterials") to the design of medical devices that will lead to notable clinical, surgical, diagnostic or therapeutic advances. This is essential for promoting the growth of this sector and addressing the ever-increasing needs of society.

The core of this handbook (Chaps. 3–15) is devoted to explaining novel design and manufacturing technologies and strategies with impact on the biomedical field, while Chaps. 16–18 summarised the knowledge acquired along this handbook for

implementing more adequate systematic methodologies oriented to biodevices. Several concepts covered in present chapter will be detailed further on in such last chapters.

Standards Summary

Main Organisations

- International Organization for Standardization "ISO" (www.iso.org)
- The World Medical Association (www.wma.net)

"New Approach" Directives Related to the Medical Industry

- Directive 93/42/EEC related to "medical devices"
- Directive 90/385/EEC related to "active implantable medical devices"
- Directive 98/79/EC related to "medical devices for "in vitro" diagnosis"

Standards Related to the Development of Medical Devices

- ISO 10993 standard on "biological evaluation of medical devices"
- ISO 13485 standard on "sanitary products, quality management and regulatory affairs"
- ISO 13488 standard on "quality systems, medical devices, sanitary products and especial requirements for applying ISO 9002 standard"
- ISO 14971 standard on "application of risk management to medical devices and sanitary products"
- ISO 15223 standard on "symbols used for labelling and information provided together with medical devices"

Standards and Associations Related to Medical Imaging

- DICOM standard (Digital Imaging and Communications in Medicine): strategic document (http://medical.nema.org)
- Medical Imaging and Technology Alliance (www.medicalimaging.org)
- NEMA (The Association of Electrical and Medical Imaging Equipment Manufacturers) (www.nema.org)

Additional Documents of Interest

- Council of Europe "Convention for the protection of Human Rights and dignity of the human being with regard to the application of biology and medicine: Convention on Human Rights and Biomedicine" (1994)
- UNESCO "Universal Declaration on the Human Genome and Human Rights" (1997) and "Guidelines for Implementation" (1999)
- World Medical Association "Declaration of Helsinki. Ethical principles for medical research involving human subjects" (current revised edition 2008)

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