Chapter 2
The Role of the Engineer and Technology in Healthcare

Joerg Vienken

Abstract The engineer in charge with developing, producing and marketing of medical devices has to be a specialist in many interdisciplinary realms, ranging from natural sciences to finances and ethics. This requires both curiosity, knowledge and the capability of finding compromises in terms of cost and time. Current main issues represent the following questions: (1) "How to test a device adequately?" (2) How to cope and avoid extractables from polymers and medical devices? (3) How to achieve a reasonable biocompatibility? A good understanding of physiological pathways and processes in the body of a human being helps to answer these questions during conception, research and development of devices for medical application. Last but not least, the bioengineer has to be communicative, because many questions can only be answered in a cooperation between scientists and engineers from both academia and industry.

Introduction

Medical device technology has made an enormous progress in recent years. Diseases can be recognized earlier and therapies initiated faster and more efficiently. It can be explained by both a better understanding of the medical background and knowing the physiological consequences of medical device interaction with parts of the human body. Further, new concepts on improving quality of production and control, cost efficiency and where, when and how to apply medical devices (e.g. invasive or non-invasive) have been advanced and perfectioned. However, a "one-fits-all" medical device does not exist. The patient as a target has to be properly defined and her/his individual needs precisely addressed. It's general knowledge that when looking at possible targets for treatments with medical devices, individual properties of patients in terms of age, gender, possibly genetics and individual malfunctions of the body, have to be recognized. A short overview about functional disorders depending on patient age is provided in Fig. 2.1.

J. Vienken (✉)
Usingen, Hessen, Germany

C. Boccato et al. (eds.), *Medical Devices*, Research for Development,
https://doi.org/10.1007/978-3-030-85653-3_2

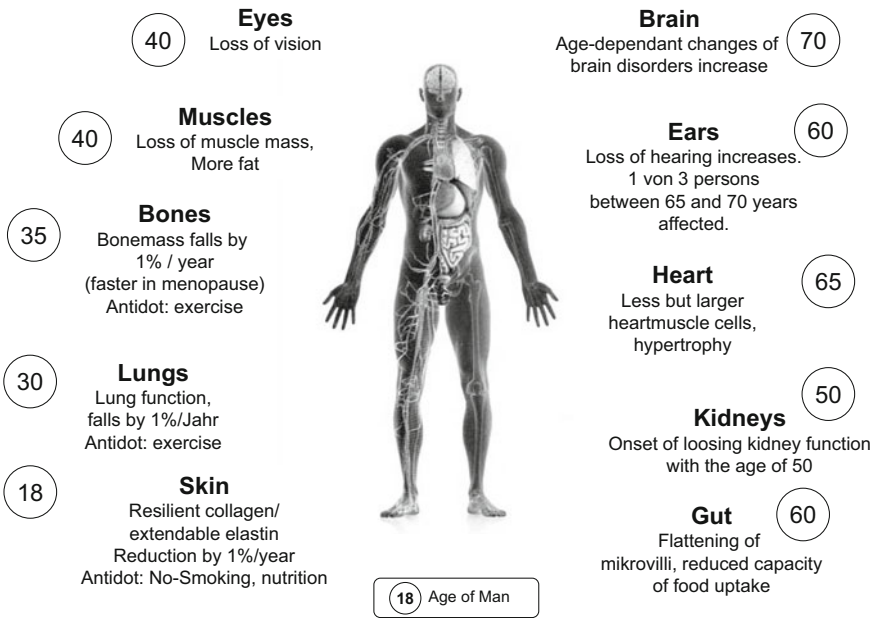

Fig. 2.1 MedTech targets based on the human time-axis. Subsequent failures of body functions are shown. Already at the age of 18 possible therapies to be addressed by medical devices or medicinal drugs may be needed to recover skin failure or for patients at an average age of 50 with first signs of kidney failure. (©: the author)

Bioengineers, who want to apply medical devices for the compensation of malfunctions of body parts, must also bear in mind that the physiology of a patient changes with age. It renders the pre-emptive development of medical devices difficult.

Recently developed innovative techniques with appropriately adapted medical devices have also shown that medical devices are available like body's spare parts. To mention only two of the most spectacular recent developments: an electronic skin which shows both flexibility and a sense of touch, possibly to be applied for the treatment of heavy wounds [1] (and not from the age of 18 onwards (see Fig. 2.1)) and brain-computer interfaces (BCIs) for the communication of people, who have lost the ability to move or speak [2]. Such BCIs help to welcome handicapped people back to a social life by "decoding attempted handwriting movements from neural activity in the motor cortex and translating it to text in real time" [2]. New trends have advanced the use of controlled device performance by an online feedback control through the direct interaction of sensors and monitors. With Artificial Intelligence (AI) techniques, information on sicknesses of global patient cohorts is stored, collected and interpreted as big data. Paralleled epidemiological investigations allow for the prediction of diseases now and in the future, which will possibly allow to predict the needs of medical devices, their properties and performances in times to come.

A promising example stems from the international databank MONDO (Monitoring Dialysis Outcomes across the world [3]). With the retrospective analysis of a huge cohort of patients on haemodialysis, a close relationship between the rise in concentration of an indicator for inflammation (C-reactive protein) and subsequent death could be proven. This allows to ask the question, whether the kinetics of inflammatory signals [4] or the control of fluid status [5] in the time course of a chronic diseases could be influenced by the use of innovative medical devices in order to avoid or delay premature death. Future investigations and innovations will certainly guide us towards this direction.

2.1 Medical Devices, Experiences Skills, Customer Needs and Ethical Impacts

Medical devices and the goal to adapt engineered developments to the individual needs of patients have a long history. It is based on skills and experiences of engineers in collaboration with physicians. In an Egyptian tomb, a wooden big toe prosthesis was discovered which represents possibly the oldest known intravital limb prosthesis [6]. It belonged to a woman, possibly a princess, who died at the age of 55 around 3000 years ago. The prosthesis was artistically shaped and carved with a toenail. Recent investigations have further shown, that the wooden prosthesis had been modified, possibly to be adapted to the specific needs of the female customer. Later in history, physicians experienced the amputation of lower legs and the subsequent leg-support by a prosthesis. For instance, the Christian mythology reports on a leg amputation on a white patient and its replacement by the leg of a black person. The protagonists in charge had been the courageous holy saints Cosmas and Damian [7]. However, to be unconventional and not keeping with the times, their expert behaviour represented a risk of death for such surgeons. Mythology tells us that they have been decapitated later.

Medical therapies have never been for free. A woodcarving from the year 1517, showing the amputation of a lower leg by a barber surgeon, reveals that the operation was controlled by a supervisor standing next, who hold out his hand for a timely compensation [8].

To date bioengineers in charge of developing a medical device may profit from the past and consider those experiences on technology, customer needs, ethical behaviour and cost. These basic conditions have not changed until to date. Despite being sick, the patient remains to be a customer, who is entitled to request excellent performance, reliability and reproducibility of medical devices (MDs) to be provided by the bioengineer. Thus, the knowledge of an engineer in the MD realm has to be very wide as the medical device technology is interdisciplinary. A whole lot of science disciplines are involved here, such as chemistry (polymers), physics (mechanical and electrical, flow pattern of liquids), biology and microbiology (behaviour of cells and tissue), medicine (physiology and treatment modes), hygiene

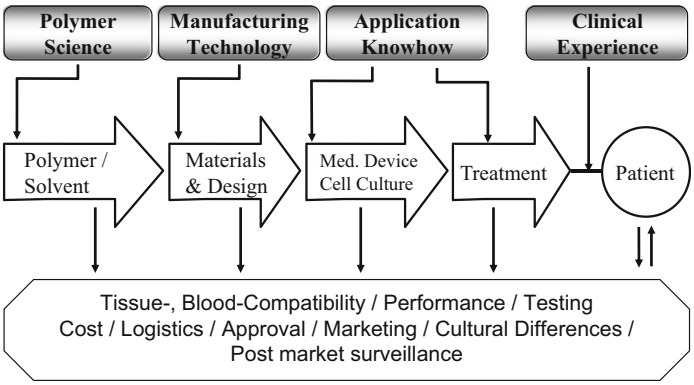

Fig. 2.2 Bioengineers, who develop medical devices, have to be universally engaged in getting knowledge in all disciplines of natural sciences and the determining bystander conditions (lower panel). When being incompetent in one or the other field, a collaboration with suitable specialists is mandatory. A cooperation between academic and industrial institutions has proven beneficial for both parties in many situations and has led to a win-win situation. (©: the author)

(microbial contamination and sterilization), clinical trial experience, certification and approval, managerial skills, as well as an experience in economics, marketing and sales (customer relationship). These requirements look highly universal and a bioengineer in charge of medical device development has to cope with it. Given that this is not achievable for all disciplines, a close collaboration between specialists in different realms will come out successful and include the cooperation between industrial and academic institutions. Therefore, medical device technology is both, interdisciplinary and intercommunicative. Bioengineers, who develop medical devices, are thus also mediators between the above-mentioned disciplines. Figure 2.2 depicts these bioengineering realms (upper panel), developmental chains (centre) and the determining bystander conditions.

2.2 Challenging Issues for Engineers: Reliability of Medical Device Testing

The current market for medical devices is a global business. The involved industry represents not only national interests but has also to face international regulations. No wonder, that customers and patients have to be addressed under varying global aspects. It implies that a “standard customer” or a “standard patient” to whom medical devices are delivered and administrated does not exist. Local conditions, ethnic peculiarities or genealogic facts have to be taken into account, when medical devices are conceived, developed and marketed. New concepts for the application of medical devices are based on the principle of “pay-for-performance”. The capability to measure the corresponding performances thus becomes the number one

requirement. A commonly expressed statement indicates accordingly: "You can only control, what you can measure!" During both research and development of medical devices, as well as during clinical trials for approval, the performance of an instrument and its components (polymers, glues, paintings, codes) have to be assessed under bystander conditions in order to cope with the peculiarities related to age, gender, different ethnics and varying genetical factors. It is interesting to mention in this context that many authors of scientific publications on clinical trials in the USA discriminate between Blacks, Hispanics and Whites. Obviously, such a differentiation is necessary to explain variable results between such cohorts.

2.2.1 The Problem

"Methodology is everything and the devil is in the details!" is a remark of Paul Simmons, the past president of the International Society for Stem Cell Research, in an article in Nature Magazine [9]. P. Simmons refers here to current problems related to the reproducibility of data in stem cell research. Do we have to consider similar thoughts, when speaking about medical devices and their reproducibility? We should not anticipate fraud or manipulation, when data or analyses on the performance of comparable medical devices which are available in the public literature or in scientific publications, differ considerably. In addition, and to the surprise of precisely thinking engineers, evaluations from in vivo comparisons of medical devices or other products in life sciences show standard deviations of up to 100%. This is by far higher than comparable results from common engineering investigations. Obviously, in life sciences impact factors, such as the specific role of an individual patient, the day time of measurement, comorbidities and medication play a determining role. Decisions to be taken by engineers during the time course of developing a medical device have to take these observations into account. Recently and in this context, the allegoric term "Death Valley" was introduced into the field of medical device technology. The term is understood to paraphrase the huge discrepancy between published results from either academic or industrial research.

A medical device must be competitive, functional and reliable. These attributes are usually targeted in preclinical and clinical trials. A low reproducibility and a lack of safety of recently developed medical devices in preclinical investigations corresponds to unfavourable high economic losses, a delayed way to market and a loss of reputation. One of the underlying motives of the new European Medical Device Regulation (MDR) "Better safe than sorry!" reflects the responsibility of engineers to achieve these goals. On the other hand, products originating from academic research and described in scientific publications do not necessarily have to cope with these regulations, as long as they have not been approved. An analysis of scientific articles, which has been published in the journal *PLoS Biology* in 2015, shows that about 50% of published scientific data on medicinal products are not reproducible. As a consequence, economic losses in the referred medical industry added up to 28 billion

US-$. In addition, affected patients were highly disappointed about non-available medical devices [10].

2.2.2 Reasons and Explanations

The above considerations influence decision makers especially in the early phase of medical device development. What can be done to overcome these headache-like situation? A series of factors play a role which have to be identified and compensated by knowledge and both quality and perfection of analytical test systems. For instance, blood/tissue/material- or blood/tissue/ device-interaction play a considerable role during tests of device performance, e.g. when comparing samples from young or elderly persons. In addition, the purity of raw materials, the stability of polymer blends deriving from different sources, packaging materials and the type of device sterilization cannot be neglected. In addition, in vitro testing of materials and devices in the early phase of development is usually performed with blood from healthy donors. The quality of such a liquid for testing depends on the type of donor, his age, gender, possible pre-existing illnesses, circadian influences of blood drawing, and the actual nutrition and medication. For instance, a fatty meal on the evening before donation or the intake of Aspirin affects blood behaviour and test results considerably. As a consequence, standardization of test procedures is a *conditio sine qua non* and knowledge of possible pitfalls, as well as a careful documentation of results, including the hour of experiment completion, is absolutely necessary. The precise selection of tests, as recommended in ISO 10993-4 [11], may help the engineer to be on the safe side for drawing conclusions on performance of materials and devices.

2.2.3 Boundary Conditions for Optimal Testing

Some examples may further illustrate the above statements.

1. The adhesion of platelets to material or device surfaces depends on the respective temperature. This is not surprising. However, differences can be observed, when polymers of varying composition are submitted to experiments and measurements under either room temperature (22 °C) or body temperature (37 °C). Current observations in in vitro experiments have not shown yet any differences [12]; however, in vivo analyses are still pending.
2. It is common practice to test with healthy donor blood, whereas the upcoming clinical application will happen under pathological conditions. As an example, the performance of blood varies considerably when exposed to different shear rates or when in contact with different polymers during perfusion experiments. In detail, blood when donated by diabetic patients, patients with coronary artery

disease or healthy donors shows different levels of fibrinogen or other peptides. This may serve as an explanation for this observation [13].

3. Recent results have shown that platelet derived microparticles (PMPs) emerged as a novel regulator of vascular dysfunction. PMPs are extracellular vesicles released from activated platelets and are found to be widely deposited in podocytes of glomeruli both in diabetic patients and animal models. Their presence is closely associated with the progression of diabetic nephropathy [14]. PMPs are also defined as "micro-vesicles" and contain mRNA and could be thus also applied for medical therapies [15]. Given that PMPs of different patients are generated by the interaction of platelets with devices during perfusion of blood, clinical sequelae—in a positive or negative way—can be expected also during in vivo application. With a pre-emptive analysis of donor blood, consequences of blood/material/device interaction could be understood and interpretations for an engineer made easier.

2.2.4 Conclusion on Testing

The statement "Who cures is right!" should be replaced by "Who measures is right!" during research and development of medical devices. Preclinical in vitro and clinical in vivo test-experiments require a stringent standardization [16]. When using blood as a solution for test-experiments, specific properties of donors, or animals either healthy or sick, should be taken into account [17].

2.3 Challenging Issues for Engineers: Medical Devices and Extractables

"Blood is a very peculiar liquid", stated Mephisto to Faust in the novel "Faust" by the German writer Johann Wolfgang von Goethe. Indeed, blood, which contains electrolytes, enzymes, lipids and proteins apart from water, is capable of extracting leachables from polymers or medical devices in a highly efficient manner. Consequently, biomaterial testing should always examine extraction capacity with the help of appropriate extraction media. One reason for the occurrence of extractables is a shift to a broader molecular weight (MW) distribution during polymer synthesis (Fig. 2.3). Broader MW-distributions give rise to a higher susceptibility of the resulting polymer for extractables.

Polymer ageing adds to the source of extractables as well as the degradation of some polymers in a wet atmosphere or after some sterilization procedures. Medical devices undergo degradation processes given that they are implanted for a long-term period in the human body. This also holds true for those chronic patients who are treated by extracorporeal blood purification systems, such as haemodialysis. Here, medical devices are chronically exposed to blood, serum or interstitial liquids that

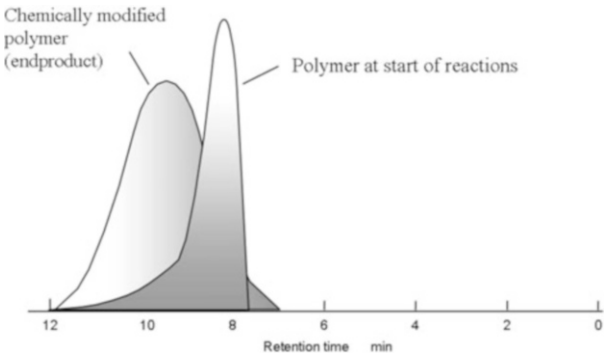

Fig. 2.3 Molecular weight distribution of a polymer before and after the chemical reaction assessed by gel permeation chromatography (GPC) analysis. A wider molecular weight distribution (left) gives rise to a higher level of extractable oligomers. (©: the author)

provoke polymers to be degraded, saponified in the case of ester compounds or promote the release of spallation particles as observed in the case of silicon tubing. During the development of new medical devices, engineers should thus focus on possible degradation products that may be released from polymeric material into body tissue, blood or organs to avoid long-term complications.

2.3.1 How are Extractables Defined?

Extractables are chemicals that are generated under exaggerated temperature and time conditions in the presence of an appropriate solvent. **Leachables** are chemicals that migrate spontaneously from a container-closure system (e.g. blister), from packaging components and/or from processing equipment under recommended or routine conditions of use and storage. Leachables are often a subset of extractables.

Adverse clinical reactions initiated by extractables are not exclusively found after the exposure of polymers to human blood or tissue. Even metallic devices, which are generally considered to behave neutrally, are able to provoke adverse clinical reactions as shown by the following example.

2.3.2 Case Report on an Artificial Hip

A year and longer lasted the problems of a patient, when his physicians discovered a cobalt intoxication originating from a previously implanted artificial hip. The patient suffered from severe heart failure and both fever with unknown origin and enlarged lymph nodes. A careful anamnesis revealed that the patient's ceramic-on-ceramic hip prosthesis had been replaced by a metal-on-polyethylene prosthesis around

15 months before. Laboratory analyses showed a nearly 1000-fold increase in the concentration of cobalt and chromium ions in his blood, combined with some metal debris at the left-sided hip. Obviously, remaining ceramic particles from his first prosthesis have destroyed the metal head of the hip replacement [18] and had led to these deleterious findings.

Chronically sick haemodialysis patients are another cohort, that may suffer from leachables released into their organism. Dialysis patients are repeatedly exposed to an extracorporeal blood circuit that is made up from tubing, syringes and filters for many years. By this means, extractable materials may accumulate in the body of these patients and induce adverse clinical effects. In recent years, this treatment has reached perfection by using pure raw materials, avoiding the release of components from medical devices, e.g. a special type of plasticizer. However, it can be expected that effects based on extractables will increase in number, given the rise in the number of dialysis patients in recent years. For instance, in Japan more than 25,000 patients are currently undergoing this therapy already for more than 20 years [19]. Thus, leachables originating from the dialysis system, in particular from polymers in the extracorporeal blood circuit are now a matter of interest.

2.3.3 Observations from Experiences on Haemodialysis Treatments

The extracorporeal blood circuit used for dialysis therapy is engineered from polymers representative for most medical devices, such as polycarbonate, silicone, polypropylene (PP), polysulphone (PSu) and polyurethane (PUR). During medical application, these polymers are exposed to body liquids, such as plasma or whole blood. Apart from blood cells, both, human and animal blood contains water, electrolytes, proteins, hormones, and enzymes (Table 2.1). Due to these compounds, both, "blood plasma" or "whole blood" are able to wet any biomaterial independent of its chemical composition, whether hydrophilic, hydrophobic or with an amphiphilic domain-like surface. Blood in contact with biomaterials offers an ideal chemical environment for extracting substances from bulk polymers, e.g. oligomers or biodegradable compounds. Body liquids possess ideal solvent-like properties. As a consequence, leachables may accumulate in the body, in particular in the body of long-term chronically exposed patients.

In its revised edition from 2009, ISO 10993-1 recommends to consider extractables and degradation products during the biological evaluation process of medical devices [20]. Problems arise, however, how to simulate the extractive capacity of blood? ISO 10993-12 (Art 4) provides the answer: "the solvent selected as extractants shall: (a) be suitable for use in the specific biological test system; (b) simulate the extraction which occurs during clinical use of the device and/or (c) maximize the amount of the extract".

Table 2.1 Blood is composed of plasma and cells

Plasma (> 1300 compounds)	**Blood cells**
1. **Proteins (8%)** Among others: – Albumin (50%) – Immunoglobulins (antibodies, 35%) – Fibrinogen (5%) 2. **Water** 3. **Inorganic salts**; electrolytes 4. **Further compounds** Hormones, fat, carbohydrates, enzymes	1. **Erythrocytes** (red blood cells, 4–5 × 10^{12}/L) 2. **Thrombocytes** (platelets, 150–380 × 10^{9}/L) 3. **Leukocytes** (white blood cells, 6–8 × 10^{9}/L) (T-cells, B-cells, granulocytes, polymorphonuclear cells, eosinophils, macrophages, monocytes, killer-cells)

Plasma contains water and fat, electrolytes, carbohydrates, proteins and enzymes. This composition allows for wetting surfaces of all biomaterials and devices, independent of their chemical composition, either hydrophilic or hydrophobic. Blood and other body liquids are perfect media to provoke the extraction of any loosely bound material or polymeric contaminants

The following media for extraction are suggested and one per type should be subsequently and not exclusively used in an extraction experiment:

1. Polar solutions (water, saline (0.9% NaCl in water), culture media without serum).
2. Unpolar solutions (vegetable oil, e.g. Sesame oil).
3. Additionally: polyethylene glycol (PEG 400), dimethyl sulphoxide (DMSO), culture media with serum, alcohol/water mixtures.

Experiences in my laboratory have shown that mixtures of 20/100% EtOH/H_2O provide optimal results when a transparent solution is needed to simulate the behaviour of blood.

Further, a practical guide and scheme for testing medical devices is provided in ISO 10993-17 [21]. Allowable limits for leachable substances in biomaterials are addressed in ISO 10993-12 [22].

2.3.4 Examples for Adverse Clinical Effects in Patients

Already in the 1980s, leachable ethylene-oxide (ETO) after gas-sterilization of medical devices, provoked severe allergic reactions in hypersensitive patients. Physicians defined these reactions as a “first-use syndrome”, because they disappeared either after a careful rinsing or after re-use of the device. ISO 10993-7 refers to maximum allowable ETO-residuals [23]. Further, some compounds, such as the plasticizer Bis(2-ethylhexyl)-phthalate (DEHP) or residuals from polycarbonate (PC), polysulphone (PSu) or some resins, such as Bisphenol A (BPA) or Bisphenol S (BPS) may interact with hormone receptors at the surface of biological

cells. By this means hormone-like signals are induced after the leaching of BPA and BPS from medical device polymers. Although DEHP and the bisphenols are not hormones, they are called "exogenous hormones" or "endocrine disruptors" due to their hormone-like capacity to bind also to hormone receptors. According to the EU, DEHP meets the criteria for classification as toxic for reproduction (category 1B) in accordance with regulation (EC) Nr. 1272/2008 and should thus not be present in medical devices applied to adolescents and breast-feeding women, among others [24].

Leachables may also be found to occur during the ageing process of polymers. This is a further argument in favour of an **expiry date** for medical devices. Scientists from the US Centers for Disease Control, Prevention and Radiological Health (CDC) reported in 2000 [25] that a severe and unusual outbreak of serious neurological signs and symptoms occurred in 5 out of 7 patients in association with the use of 10-year-old dialysers with passed expiry dates. All patients exposed to these filters developed an acute onset of diminished vision and hearing. Four case patients never recovered. The authors explained these findings with material degradation of the cellulose-acetate polymer, as the average molecular weight decreased from 40,000 to 30,000 in the dialysers tested and referred to either de-acetylation (saponification) or chain scission of the polymer [25].

To the surprise of many medical device manufacturers, even quality management measures, if not carefully prepared, may result in fatal incidences. As reported in a series of publications in 2001 and 2002, 23 dialysis patients died in Croatia as a consequence of the repair of a medical device (dialysis filter) in the production process realized with a performance test for leaky capillary membranes: the test was performed with the help of a perfluorocarbon-5070 liquid [26]. Residual amounts of PF5070 stayed in the filter and were rinsed out by the perfusing blood during the subsequent dialysis therapy. PF5070 slowly accumulated in heart and lungs of the patients where it caused their death several hours later by foam formation.

2.3.5 Conclusion on Extractables

Leachables and extractables from polymers, biomaterials and medical devices should be carefully assessed, once they are exposed to body liquids in long-term clinical application. Associated adverse events may lead to severe allergic reactions or even fatal consequences. The amount of residual extractables in medical devices should, thus, be kept as low as possible. Open questions, however, still remain to be answered, e.g. what are the threshold levels for leachables below which no adverse events can be detected? Or: "How to control the release of leachables in long-term chronic patients?" As long as these questions remain open, careful clinical observations and a detailed understanding of the underlying mechanisms is mandatory.

2.4 Challenging Issues for Engineers: Medical Devices and Biocompatibility

Bioengineers in charge of medical development have to be familiar with device properties in terms of biocompatibility pattern, because devices in contact with body structures may provoke physiological reactions. Surface reactivity and intrinsic properties of biomaterials and devices determine device- or material-biocompatibility. However, the term "biocompatibility" has turned out to become a buzzword and is used in many cases without any detailed background information on the type of device, its composition and clinical application. It is reasonable to cite here the definition of the European Society for Biomaterials from 1993 to have a closer insight:

> "Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application".

Consequently, biocompatibility pattern of a device cannot be generalized. These characteristics depend on the type of device, its specific application and even on the very disease or situation of a patient. When therefore reporting on the biocompatibility of a medical device, careful distinctions have to be made whilst avoiding a "generally speaking". In addition, controversies have come up how to define interactions between body liquids and materials/devices. ISO 10993-4 from 2009 [27] reflects about classification of interactions, such as:

> Interactions which mainly affect the device and *which may or may not have* an undesirable effect on the subject as follows:
>
> 1. Adsorption of plasma proteins, lipids, calcium or other substances from the blood onto the surface of the device, or absorption of such substances into the device.
> 2. Adhesion of platelets, leukocytes, or erythrocytes onto the surface of the device, or adsorption of their components into the device.
> 3. Formation of a pseudointima or tissue capsule on the surface of the device.
> 4. Alterations in mechanical and other properties of the device.

It is still a matter of debate, whether interactions *may or may not have* an undesirable effect. The authors understanding is that biocompatibility assessments should be done as close as possible to the intended clinical application, and therefore, biocompatibility pattern should describe preferentially "undesirable effects".

Investigative research has identified many factors for the assessment of biocompatibility. However, no clear-cut conclusion has been derived which of these factors would yield the most reproducible results. A short overview, provided in Fig. 2.4, shows that we have to discriminate three main areas, such as inflammation, allergy and immune system and coagulation.

In addition, Table 2.2 provides examples of medical devices and their specific characterization in terms of biocompatibility testing.

It is the intention of many investigators to obtain an overall score when assessing biomaterials or medical devices. A score could be a compromise for a fast characterization and help decision-making. Such a score has been recently developed [28].

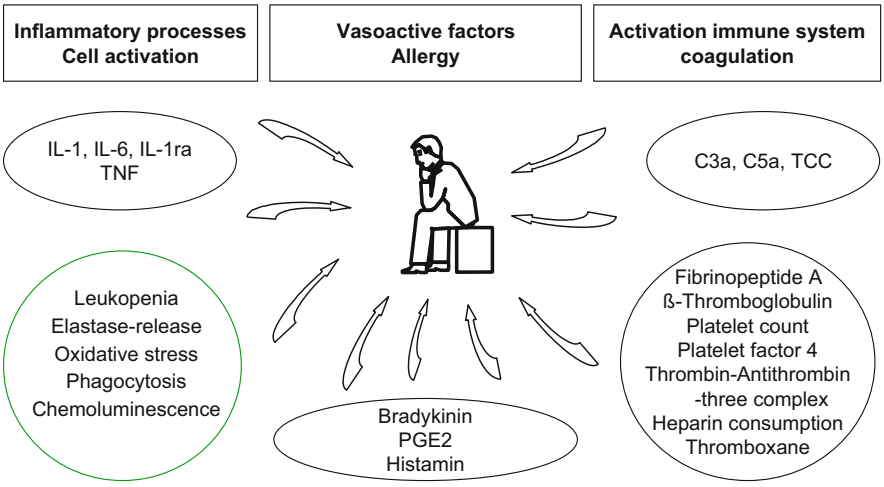

Fig. 2.4 Three main areas should be applied for the characterization and assessment of biocompatibility pattern of a material or a device: Inflammatory processes (Interleukin l, IL-1, Interleukin 6, IL-6, and Tumour Necrosis Factor, TNF), vasoactive factors (Prostaglandin E_2, PGE_2) and allergy, as well as the activation of both the immune system and the coagulation cascade. Factors representing the plasmatic immune system, i.e. the Complement System: C3a, C5a, TCC. (©: the author)

Table 2.2 Proposed features for biocompatibility testing of specific medical devices

Device examples	Thrombosis	Coagulation	Platelets	Haematology	Complement system
Atherectomy devices				x[a]	
Blood monitors	x			x[a]	
Blood storage and blood collection devices, extension sets		x	X	x[a]	
ECMO and HD systems	x	x	X	x	x
Percutaneous systems					
Catheters, guidewires, endoscopes, intravascular ultrasound, laser systems	x	x		x[a]	
Cell savers		x	x	x[a]	
Devices for adsorption of specific substances from blood		x	x	x[a]	
Donor and therapeutic Apheresis equipment		x	x	x	x

Adapted from [27]
[a]Haemolysis testing only

In the following those biocompatibility aspects of biomaterials which provoke clinical consequences are described in short.

2.4.1 Thrombogenicity and Blood Coagulation

Artificial surfaces are able to stimulate platelet activation and the coagulation cascade. Modern polymers/biomaterials exhibit a considerably reduced thrombogenic potential. Apart from chemical polymeric properties, the geometric design of flow paths, e.g. in capillary membranes or small flexible tubes and a possible contact of blood with air bubbles may affect coagulation pathways and lead to the formation of blood clots. Haemoconcentration, as observed after filtration processes, like in haemodialysis or in plasmapheresis, may further lead to the formation of blood clots. The best advanced parameter for assessing coagulation is the analysis of the Thrombin-Antithrombin III Complex (TAT).

2.4.2 Stimulation of the Immune System (Complement- and Cell-Activation)

Complement activation represents the classical parameters of biomaterial bioincompatibility. Its alternative pathway depends on the presence of nucleophilic surface moieties. Complement activation by biomaterials or surfaces depends on their surface chemistry. For instance, the presence of hydroxyl-groups (OH-groups) on a materials surface leads to an ester binding of the complement protein C3b, which initiates the autocatalytic alternate pathway of the complement cascade. A chemical modification of biomaterial surfaces through the substitution, of such hydroxyl-groups, by ester or ether groups prevents complement activation. Adverse events are mainly seen, when complement activation is twinned with the presence of endotoxins from bacterial cell walls. Here, cytokines are released in a synergistic manner from white blood cells (cell-activation), which may lead to inflammatory reactions.

2.4.3 Hypersensitivity Reactions

Allergic reactions are frequently observed in those patients, who have been in contact with residuals of the sterilizing agent ethylene-oxide (ETO). ETO is bound spontaneously to the blood protein albumin. Due to its then higher molecular weight, ETO provokes the formation of IgE-antibodies, which are responsible for the majority of seen hypersensitivity reactions. Biomaterials such as polyurethane

(PUR) and poly-methyl-methacrylate (PMMA) store ETO in their bulk structure and show a slow-release pattern. Apart from ETO, polymer extractables (e.g. oligomers) or other compounds from medical devices used in extracorporeal blood purification systems [29] are eluted with the help of blood and may induce hypersensitivity- or adverse reactions, as observed with cellulose extracts (1.4-ß-glucans), perfluorocarbons, isocyanates from PURs, or plasticizers. It is still a matter of controversy, whether these compounds are able to induce acute effects in humans or not. Clinical consequences in chronically treated patients, such as those treated with haemodialysis, however, have to be seriously considered.

2.4.4 Haemodynamic and Vasoactive Effects

Surfaces bearing negative charges of a defined charge-density stimulate the "contact phase" of coagulation. As a consequence, the vasodilator bradykinin is formed and—if not degraded by ACE (angiotensin-converting enzyme)—severe blood pressure drops are observed. This happens mainly in those patients, who are treated by ACE-inhibitors. Some polymers made from either polyacrylonitrile-blends or dextran-sulphate show these effects and have exerted fatal incidences in many patients treated by haemodialysis or apheresis [30, 31]. Similar observations can be made during reprocessing of medical devices, when oxidation of adsorbed proteins give rise to the formation of negative charges of a defined density at material surfaces.

2.4.5 Conclusion on Biocompatibility

Biocompatibility pattern have to be analysed systematically. They refer to all components of a device, such as polymers and their blends, the geometry and stability of a device itself under storage or during clinical application and last but not least to treatment modality and the specific situation of a patient (Fig. 2.5). It is possible to adapt the polymer composition of modern biomaterials in such a way that adverse patient reactions can be excluded or at least be minimized. This is the consequence of a better understanding of the underlying mechanisms of blood material interaction. In addition, both, smart geometries and design of biomaterials and avoiding sterilization with ethylene oxide gas through steam sterilization are the strategies for further biomaterial development [32, 33].

Biocompatibility pattern has to be analysed systematically. They refer to all components of a device, such as polymers and their blends, the geometry and stability of a device itself under storage or during clinical application and last but not least to treatment modality and the specific situation of a patient. This is an ideal example for the application of a system approach in medical device development.

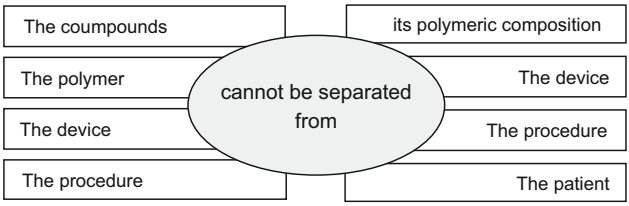

Fig. 2.5 Biocompatibility pattern has to be analysed systematically. They refer to all components of a device, such as polymers and their blends, the geometry and stability of a device itself under storage or during clinical application and last but not least to treatment modality and the specific situation of a patient. (©: the author)

Conclusion

The engineer in charge with developing, producing and marketing of medical devices has to be a specialist in many interdisciplinary realms, ranging from natural sciences and engineering to finances and ethics. This requires both curiosity, knowledge and the capability of finding compromises in terms of cost and time. Current main issues represent the following questions: (1) "How to test a device adequately?" (2) How to cope and avoid extractables from polymers and medical devices? (3) How to achieve a reasonable biocompatibility? A good understanding of physiological processes in the body of the human being helps to answer these questions during conception, research and development of devices for medical application. Last but not least, the bioengineer has to be communicative, because many questions can only be answered in a cooperation between scientists and engineers from both academia and industry.

Take Home Message

- The interdisciplinarity and continuously innovative field of medical device technology requires extended knowledge of the engineers in charge of developing such devices.
- Development of devices needs to apply adequate and standardized testing procedure not neglecting the special physiological properties of a sick patient.
- Extractables from materials and devices play an important role in safety and stability considerations of medical devices.
- Biocompatibility of materials and devices directly affects the patient's well-being.
- A close cooperation and communication between academia and industry helps to answer unsolved questions.

References

1. Sanderson K (2021) Electronic skin: From flexibility to a sense of touch. Nature 591:685–687
2. Willet F, Avansino D, Hochberg L, Henderson J, Shenoy K (2021) High performance brain-to-text communication via handwriting. Nature 593:249–254
3. von Gersdorff G, Usvyat L, Marcelli D, Grassmann A, Marelli C, Etter M et al (2013) Monitoring dialysis outcomes across the world – The MONDO global database consortium. Blood Purif 36:165–172
4. Usvyat L, Barth C, Bayh I, Etter M, von Gersdorff G, Grassmann A et al (2013) Interdialytic weight gain, systolic blood pressure, serum albumin, and C-reactive protein levels change in chronic dialysis patients prior to death. Kidney Int 84:149–157
5. Dekker M, Marcelli D, Canaud B, Carioni P, Wang Y, Grassmann A et al (2017) Impact of fluid status and inflammation and their interaction on survival: A study in an international hemodialysis patient cohort. Kidney Int 91:1214–1223
6. Samples R (2001) Mummy has a wooden toe. Science 291:243
7. Becker C (1914) Die Wunderheilung der Ärzteheiligen Cosmas und Damian. Dtsch med Wschr 40:27–28
8. Hans von Wechtlich (1517) Feldtbuch der Wundartzney. Strassburg 1517
9. Check E (2007) The hard copy. Nature 446:485–486
10. Freedman et al (2015) The economics of reproducibility in preclinical research. PLoS Biol 13(6):e1002165
11. International Standard Organisation (2009) (DIN EN ISO) 10993–4. Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood
12. Braune S, Fröhlich G, Lendlein A, Jung F (2015) Effect of temperature on platelet adherence. Clin Hemorheol Microcircul 61:681–688
13. Braune S, Groß M, Walter M, Zhou Z, Dietze S, Rutschow S, Lendlein A, Tschöpe C, Jung F (2016) Adhesion and activation of platelets from subjects with coronary artery disease and apparently healthy individuals on biomaterials. J Biomed Mater Res Part B 104:210–217
14. Zhang Y, Ma K, Gong Y, Wang G, Hu Z, Liu L, Lu J, Chen PP, Lu CC, Ruan X, Liu BC (2018) Platelet microparticles mediate glomerular endothelial injury in early diabetic nephropathy. J Am Soc Nephrol 29:2671–2695
15. Cantaluppi V, Gatti S, Medica D, Figliolini F, Bruno S, Deregibus M, Sordi A, Biancone L, Tetta C, Camussi G (2012) Microvesicles derived from endothelial progenitor cells protect the kidney from ischemia–reperfusion injury by microRNA-dependent reprogramming of resident renal cells. Kidney Int 82:412–437
16. Vienken J (2010) Biomaterials for medical devices: are current hemo- or biocompatibility tests adequate? Mat Wiss u Werkstofftech 41:1081–1085
17. Mueller X, Tevaearai H, Jegger D, Tucker O, von Segesser L (2001) Hemolysis and hematology profile during perfusion: Inter-species comparison. Int J Artif Organs 24:89–94
18. Dahms K, Sharkova Y, Heitland P, Pankuweit S, Schaefer R (2014) Cobalt intoxication diagnosed with the help of Dr. House. Lancet 383:574–575
19. Nitta K, Goto S, Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, Nakai S, Wada A, Hamano T, Hoshino J, Joki N, Abe M, Yamamoto K, Nakamoto H (2020) Annual dialysis data report for 2018, JSDT Renal Data Registry: survey methods, facility data, incidence, prevalence, and mortality. Ren Replacem Ther 6:41
20. ISO 10993-1 (2009) Biological evaluation of medical devices: Part 1. Evaluation and testing within a risk management process
21. ISO 10993-12 (2003) Biological evaluation of medical devices: Part 12. Sample preparation and reference materials
22. ISO 10993-17 (2002) Biological evaluation of medical devices: Part 17. Establishment of allowable limits for leachable substances. (New ISO under development 2021)
23. ISO 10993-7 (2009) Biological evaluation of medical devices: Part 7. Ethylene-oxide sterilization residuals. Edition 2009

24. Commission regulation (EU) Nr. 143/2011 of 17 February 2011. Off J European Union, L44/2 from February 18, 2011
25. Hutter J, Kuehnert M, Wallis R, Lucas A, Sen S, Jarvis W (2000) Acute onset of decreased vision and hearing traced to hemodialysis treatment with aged dialysers. JAMA 83:2128–2134
26. Canaud B, Aljama P, Tielemans C, Gasporovic V, Gutierrez A, Locatelli F (2002) Performance liquid test as a cause for sudden deaths of dialysis patients: perfluoro-hydrocarbon, a previously unrecognized hazard for dialysis patients. Nephrol Dial Transplant 17:545–548
27. ISO-Standard 10993–4 (1993) Biological evaluation of medical devices
28. Erlenkötter A, Endres P, Nederlof B, Hornig C, Vienken J (2008) Score model for the evaluation of dialysis membrane hemocompatibility. Artif Organs 32:962–968
29. Gwinner W, Menne J, Lonnemann G, Bahlmann F, Koch K, Haller H (2005) Life-threatening complications of extracorporeal treatment in patients with severe eosinophilia. Int J Artif Organs 28:1224–1227
30. Tielemanns C, Madhoun P, Lenaers M, Schandene L, Goldman M, Vanherweghem JL (1990) Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. Kidney Int 38:982–984
31. Kammerl M, Schaefer R, Schweda F, Schreiber m, Riegger G, Krämer B (2000) Extracorporeal therapy with AN69 membranes in combination with ACE-inhibition causing severe anaphylactoid reactions: still a current problem? Clin Nephrol 53:486–488
32. Vienken J (2001) Polymers in dialysis: characteristics and needs. Med Device Technol 12:18–27
33. Vienken J, Bowry S (2002) Quo vadis dialysis membrane? Artif Organs 26:152–159