Chapter 1

Introduction

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In modern medicine, technology plays a prominent role in the diagnosis of diseases and treatment of patients. As a consequence, healthcare requires new generations of medical doctors and engineers: medical doctors who are familiar with the latest technical developments in their field, and engineers who have knowledge about the human body-anatomy, physiology, pathology, etc. Development of medical products requires a close cooperation between doctors and engineers. Product development is a multidisciplinary and time consuming activity. In this chapter, the artificial kidney and silicone breast implants are described from a historical perspective to emphasize the long development times of medical devices. A list of medical grade materials is enclosed in the Appendix of this book.

The student should be able to explain why BioMedical Engineering is a multidisciplinary research area by its definition, and should understand the meaning of an innovation, a biomaterial and the role of medical doctors and engineers in medical product development.

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Introduction

Biomedical engineering (BME) is an multidisciplinary field that spans interdisciplinary boundaries and connects the engineering and physical sciences to the biological sciences and medicine in a multidisciplinary setting, to develop or apply new technologies in patient-oriented research and clinical healthcare. The scope of this rather young field of science covers many different medical applications, varying from the development and application of new medical imaging techniques (MRI, PET, X-ray scanning, etc.) and biochemical test kits for the assessment of organ function, cell function, cell-material interactions, blood-material interactions, to the development of medical devices like orthopedic implants, blood purification devices, mechanical circulatory support systems, etc. In tissue engineering and regenerative medicine, engineering techniques are used to facilitate culturing of cells outside the body or for changing the behavior of cells.

Due to the multidisciplinarity of BME, optimal communication between medical and technical specialists is of utmost importance. It seems that medical doctors and engineers speak different languages: doctors use terms and definitions which are often based on Latin words, while engineers like to use chemical or mathematical formulas in their language. Examples of the different communication barriers that have to be overcome are schematically demonstrated in Fig. 1, in which the development of a medical device is schematically presented as a cycle of activities.

In order to develop a new device that can be applied clinically, extensive communication is required between the potential user (the clinician) and the developer (the engineer). Whenever the developer does not understand what the user needs, the chances are high that the developed product will never find its way to the medical market. In the idea phase, new concepts have to be generated and initial sketches must be transformed into technical drawings. In this phase, communication among the engineers of different backgrounds — biomechanics, materials science and electrical engineering — is needed to build a first prototype. Often, new test set-ups have to be developed and built to

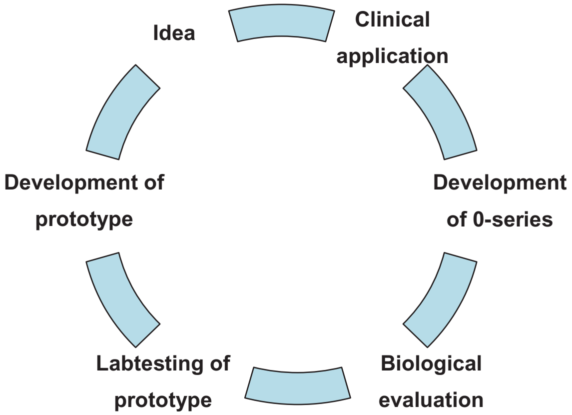

Fig. 1. Scheme of the different phases of the development of a medical device: from idea to clinical application. The curved blocks resemble the communication barriers that have to be overcome in order to realize the following product phase.

test prototypes on their functionality. Also, based on the potential risk of hazard, medical devices are classified into risk classes I, IIA, IIB and III. Depending on its contact with the skin or with other tissues or blood, and the duration of this contact, a number of biological tests (cell cultures and animal experiments) are required to prove the biological safety of the novel product. In the biological evaluation phase, communication between engineers, biologists, veterinary surgeons or clinicians is needed to define how these tests can best be performed and how the results should be interpreted. Once the technical requirements of the university prototype have been met, a small series production is needed to obtain a number of identical prototypes for animal studies. Generally, universities have to decide at this stage of development whether and when they want to transfer the developed technology to the industry. After technology transfer, the industry will have to develop its industrial prototypes, using its own manufacturing techniques to build a safe and affordable product. Furthermore, a clinical protocol has to be defined and must be evaluated by a medical ethics committee and national healthcare institutions for the purpose of obtaining permission for a first clinical application. For a clinical study, insurance has to be arranged, technical files have to be completed, and the study has to be documented and reviewed. Finally, when a new medical device has been applied clinically in a number of patients (phase-1 study), the industry can apply for CE certification or FDA approval and introduce the device on the medical market.

It does not need much imagination to understand that medical product development is a long lasting process. For example, it took more than 12 years of development time before the heart assisting blood pumps, like the Novacor® (developed at the Stanford University, USA) and the Pulse-Cath® (developed at the University of Groningen, The Netherlands) were introduced on the market. New pharmacological products need even more time before doctors can prescribe them to treat diseases. If one would like to develop a new device, using new non-medical grade materials, one may have to deal with the timespan that is needed to prove that the material is safe, as well as with the timespan to prove that the new application is safe. This is the reason why many chemical companies prefer to modify the surface characteristics of their produced materials with coatings, instead of developing new materials from scratch and have these certified for medical application. The long timespans needed before a product can be marketed pose a severe risk that once the device or medicine is introduced on the market, the technology used has become outdated already. In Fig. 2, the milestones in the development of the artificial kidney are listed. The timespan between the initial idea of using diffusion and osmosis by Thomas Graham (1861) for the detoxification of bodyfluids and the first clinical application of the artificial kidney by Willem Kolff (1946) was 85 years. The first device was introduced on the medical market 10 years later (Brigham-Kolff kidney). In the case of the artificial kidney, the clinical application depended strongly on the availability of biocompatible materials (cellophane, cuprophane), machine techniques (rotating drum, coil technique) and new anticoagulants (heparin).

Reduction in the development time may be achieved by employing management techniques. With project management, the development of a product is divided into different tasks and timeframes in which certain activities are scheduled to take place, with the tasks each allotted a certain amount of money. When the different tasks can be performed at the same time, the so-called concurrent engineering method,

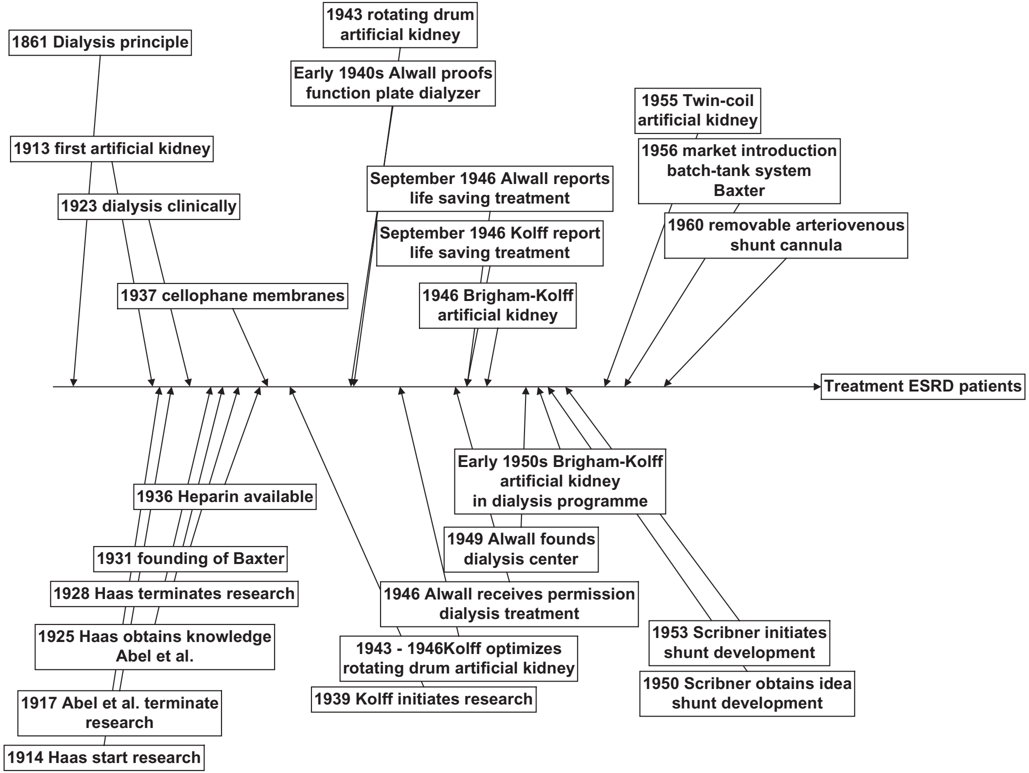

Fig. 2. Overview of the milestones in the development of the artificial kidney (Cijsouw *et al*., 2005).

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the development time will be much shorter than when all the tasks are performed in a linear manner. Knowledge management focuses on the availability of knowledge at the right moment, on the type of knowledge (sensory, tacit, coded) and on the transfer of knowledge from one project stage to the next. Medical technology assessment (MTA) aims at defining whether a new product performs better than an existing one, or whether the introduction of a new device results in a reduction of the costs of healthcare (cost-benefit studies).

The fastest way to develop a medical device is to implement concurrent engineering techniques in the project management.

Biomedical research is performed at the frontiers of science. New products or techniques must be better than the existing ones; new ideas must be innovative and lead to innovations. Innovations can be based on copying an existing technique (imitative innovation); stepwise improvement of an existing technique (incremental innovation); or development of a totally new concept (radical innovation).

As mentioned before, medical devices are categorized according to the potential risk of harm they can induce on a human body in case of technical failure. Devices can either have no direct contact with the skin or other body tissues (e.g. X-ray machine), or have contact with the skin or other body parts. If there is contact, it can be a superficial contact like a bandage, a short contact with the blood stream (infusion bag), or a longtime contact with blood (heart assist device), bone tissue (bone implants) or other tissue (breast implant). Depending on the size (surface area), shape and physicochemical properties of the material, a body will activate blood cells of the immune system and/or coagulation system to protect itself against unwanted antigens. The inflammatory response may lead to rejection of an implant or blood clots may form on a blood contacting device. Some materials are more compatible with living cells than others. Materials that are suitable for contact with tissues or blood are called biomaterials. Non-resorbable biomaterials hardly induce inflammatory responses or clot formation and possess good biocompatibility properties. Resorbable biomaterials disappear from the body after mild inflammatory responses, generally through hydrolysis. Using advanced tissue engineering techniques, cultured living cells can be brought into a container where they can be kept alive and mimic certain organ functions. The first hybrid organ that has been developed and clinically applied is the bioartificial liver.

Bioreactors should be developed by biologists and biomedical engineers: bridging tissue culturing techniques with mechanical engineering and fluid dynamics.

A biomaterial is any non-drug material that can be used to treat, enhance or replace any tissue, organ or function in an organism. In this respect, the materials used for a hand or leg prosthesis in the Middle Ages and even for George Washington's dentures were biomaterials. These, of course, were in contact with the skin or mucosa surface only. The materials, with which in certain cultures earlobes or lips are enhanced since time immemorial, are biomaterials. And these are in contact with the tissue under the skin surface, in fresh wounds. The same goes for the piercing of a nostril or a glans penis, age-old customs as well.

"Biomaterials" also refers to biologically-derived materials used for their structural rather than biological properties, e.g. collagen (a protein found in the skin, connective tissues and bone) as a cosmetic ingredient. Also, carbohydrates (biotechnologically modified) are being used as lubricants for biomedical applications and as bulking agents in the food industry. A list of contemporary biomaterials is presented in Table 1.

A medical device is any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including

Table 1 A Non-Comprehensive List of Biomaterials used in (Plastic) Surgical Practice at Present and in the Past

POLYMERS – resorbable	
Caprilactone/ glycolide 90/10	Panacryl
ε-Caprolactone	
Cellulose	
Ethylene oxide	with propylene oxide: "Pleuronic F-108," block polymer "DynaGraft" poloxamer
Glycolide 60% + dioxanone 14% + trimethylene carbonate 26%: Biosyn	
Glycolide + ε caprolacton	Monocryl
Hyaluronic acid ester	Hyaff
Poly(butylene-terephthalate)-co-(polyethyleneglycol)	Poly-active, Osteo-active
Polydioxanon	PDS (tensile strength 35 days 50%, 70 dg 0%; resorption 180–210 dg)
Polyethyleenoxyde	
Polyglactin	Vicryl (90% polyglycolic acid + 10% lactic acid), Polysorb (= vicryl + coating) (tensile strength Vicryl Rapide 5 days 50%, 12 days 0%; resorption 35–42 days; Vicryl Plus tensile strength 21 days 50%, 35 dg 0%; resorption 56–70 dg)
Poly-glecapron	Monocryl (colorless: tensile strength 7 days 50%, 28 dg 0%; resorption 90–120 day)
Polyglycolic acid	Dexon
Polyglyconate	Maxon
Polyglyceride	Trilucent
Polylactic acid	PLLA
Poly L-lactic acid (PLLA) 82% + polyglycolic acid (PGA) 18% copolymer: Lactosorb screws and plates	
Poly-L-lactide + poly-D-lactide + poly-glycolide: Delta system reorbable implants for osteosynthesis	
Polyvinylalcohol	Bioinblue, injectable

(*Continued*)

Table 1 (*Continued*)

Polysaccharide	hydrogel; soluble, but very slowly degradable
Propylene oxide	with ethylene oxide: “Pleuronic F-108,” block polymer “DynaGraft” poloxamer
POLYMERS – non-resorbable	
Acrylates – copolymer of 2-hydroxyethyl-methacrylate and ethylene-dimethacrylate: soft hydrogel contact lenses	
2octyl-cyane-acrylate	Dermabond
Phenolformaldehyde	Canvesit
Polyacrylamide	Aquamid
Polyamide	nylon, e.g. Ethilon, Supramid
Poly-alkyl-imide	Bio-Alcamid
Polyaryletherketone	PAEK
Polycarbonate	
Polydimethylsiloxane	silicone
Polyester	Ethibond, Mersilene, Ticron, Surgidac
Polyester resins	
Polyetheramide	Ultem
Polyethylene	Medpor (porous, high density), e.g. chin implants
Polyethylene glycol	soluble, not degradable
Poly(glycol methacrylate) gel, armed with polyester knitted net: Hydron breast implants (1968)	
Polymethylmetacrylate	PMMA, Sulfix
Polypropylene	Prolene, Surgipro, Marlex, Bard, Aptos
Polysulfon	
Polytetrafluoroethylene	PTFE, Goretex, Teflon
Poly-urethane	PU
Polyvinylalcohol	soluble, but not degradable
Polyvinylpyrrolidone	soluble, but not degradable (MISTI (Gold) hydrogel-filled breast implants)
Trimethyleencarbonate	
ANIMAL or HUMAN DERIVED MATERIALS	
Bovine collagen	+ chondroitin-6-sulphate on a silicone rubber sheet is Integra; major component of Zyderm, Zyplast
Calf bone	
DMB (Demineralized Human Bone Matrix) – Dynagraft: putty 64% DBM, gel 37% in reverse phase poloxamer medium	

(*Continued*)

Table 1 (*Continued*)

Dura mater	
Isolagen	cultured autologous fibroblasts
Human fascia	
Hyaluronic acid	
Ox fascia	
Porcine collagen	Evolence 30
BONE REPLACEMENT	
Calcium oxide, bioglass particulates of silicon, phosphorous oxide	NovaBone
Hydroxy-apatite tetra-tri-calcium phosphate	Mimix
Tricalciumphosphate + hyaluronic acid	Chronos-inject
37% Poloxamer gel medium + 64% D(emineralized human) M(atrix) B(one)	Dynagraft
Poly(butylene-terephthalate)-co-(polyethyleneglycol)	Poly-active, Osteo-Active
CERAMICS	
Alumina	
Carbon	
Glass	
Materials based on yttria-stabilized tetragonal zirconia	
HYDROGELS	
co-polymer of methyl-methacrylate and vinyl-pyrrolidone (osmotically active)	Osmed
Polysaccharide	
METALS	
Aluminium (in alloys)	
Cobalt-chromium-molybdenum	
Nickel (in alloys)	
Nickel-titanium (memory-metal)	
Niobium (in alloys)	

(*Continued*)

Table 1 (*Continued*)

Stainless steel	
Tantalum (also unalloyed)	
Titanium	coating for silicone breast implants introduced 2002, production terminated end of 2004
Tungsten (in alloys)	
Vanadium (in alloys)	
RESINS	
(resins are polymers in cement form, e.g.:)	
Acrylic (cements)	
Poly(L-lactide) resins	
INJECTABLES - resorbable	
chitin	
chondroitin sulphate	
collagen	Zyderm I, Zyderm II, Zyplast, Resoplast (animal-derived collagen), Evolence 30
dermis	acellular human donor skin, Alloderm
gelatine	
glycosaminoglycan	Hyaluronan
human fascia	Fascian
hyaluronic acid	Acthyal, HAART, Hylaform (animal-derived (rooster combs) hyaluronic acid), Hyal-System (not cross-linked), Juvéderm (bacteria (Streptococcus Equi) derived hyaluronic acid, cross-linked by butanedioldiglycidyl ether (BDDE)), Perlane, Restylane, Reviderm (non-animal derived hyaluronic acid + dextran microspheres), Rofilan-Hylangel (non-animal derived hyaluronic acid (Hylan gel)), Touchline (not cross-linked)
polyglycolic acid	
polylactid acid	New Fill
poly(lactic-co-glycolic acid) microspheres	
polysaccharide	Hyaluronan (glycosaminoglycan), Hylan (cross-linked hyaluronan)

(*Continued*)

Table 1 (*Continued*)

polyurethane	
polyvinylpyrrolidone	as carrier in Bioplastique
polyvinyl-alcohol	Bioinblue (6% in 94% non-pyrogenic water)
tetra-methylene-diamine	
INJECTABLES – non-resorbable	
acrylamide	Reonal
dermal collagen	porcine: Permacol
carboxymethylcellulose	CMC, carrier for hydroxylapatite microspheres, Radiance
cellulose	
collagen	Artecoll (PMMA microspheres in collagen)
hyaluronic acid	Dermalive (hyaluronic acid + hydrogel-acrylate particles), Puragen
hydroxyapatite	
methacrylamide	
methacrylate	Dermalive, Metrex
methylene-bis-acrylamide	
polyacrylamide	Amazingel, Formacryl, Argiform, Aquamid (2.5% cross-linked in water), Biogel (polyacrylamide hydrogel — the monomere is teratogenic)
poly-alkyl-imide	Bio-Alcamid
poly-dimethylsiloxane (silicone)	Bioplastique
(porous) polyethylene	Medpor
poly(methylmethacrylate)	PMMA, HEMA (2-hydroxyethyl-methacrylate (1936)); Artecoll (PMMA microspheres in collagen), Arteplast (same)
poly(tetrafluoroethylene)	PTFE, teflon paste, Goretex
polivinylalcohol	Bioinblue
polivinylpyrrolidone	in Bioplastique as carrier of silicone particles
INJECTABLES – by name	
Acthyal	hyaluronic acid
Alloderm	acellular dermis of human donor skin
Amazingel	polyacrylamide
Aquamid	2.5% cross-linked polyacrylamide in water
Argiform	polyacrylamide

(*Continued*)

Table 1 (*Continued*)

Artecoll (1991)	PMMA (polymethylmethacrylate) particles (40 μm) in 3.5% bovine atelocollagen + 0.3% lidocaine HCl. (PMMA was patented in 1928)
Arteplast (19..)	is Artecoll, but with smaller PMMA microspheres (20–40 μm)
Bio-Alcamid	4% reticulate polymer of alkyl-imide in water
Biogel	polyacrylamide hydrogel
Bioinblue	8% polyvinyl-alcohol in 92% non-pyrogenic water
Bioplastique (1992)	silicone (polydimethylsiloxane) particles (100–600 μm) suspended in polyvinylpyrrolidone ("plasdone") carrier
Dermalive	40% hydroxy-ethyl-methacrylate, ethylmethacrylate in 60% hyaluronic acid
Evolence 30	atelopeptide porcine type I collagen, ribose induced cross-linking
Fascian	human fascia
Fibrel (1990)	porcine collagen + patient's plasma + ε-aminocaproic acid
Formacryl	polyacrylamide; replaced by Argiform
Goretex (1991)	expanded PTFE (polytetrafluoroethylene)
Hyal-System	hyaluronic acid
Hyaluronan	unsulphated glycosaminoglycan, a polysaccharide
Hylaform	hyaluronic acid
Hylan	cross-linked molecules of hyaluronan
Isolagen	cultured autologous fibroblasts
Juvéderm	hyaluronic acid
Juvelift	hyaluronic acid
Medpor	polyethylene
Metrex	acrylate and methacrylate spheres
Natucoll 3.5% (199..)	3.5% bovine atelocollagen + 0.3% lidocaine HCl
Natucoll 6.5% (199..)	6.5% bovine atelocollagen + 0.3% lidocaine HCl
New Fill	polylactid acid
Perlane	hyaluronic acid
Permacol	60% milled porcine dermal collagen matrix suspension in saline

(*Continued*)

Table 1 (*Continued*)

Puragen	hyaluronic acid, double cross-linking, + acrylate particles
Radiance	is Radiesse
Radiesse	is Bioform, smooth calcium-hydroxyapatite microspheres in aqueous polysaccharide (carboxymethylcellulose) gel
Reonal	acrylamide
Resoplast 3.5% (19..)	3.5% bovine atelocollagen + 0.3% lidocaine HCl
Resoplast 6.5% (19..)	6.5% bovine atelocollagen + 0.3% lidocaine HCl
Restylane (199..)	hyaluronic acid
Reviderm	hyaluronic acid
Rovilan-Hylangel	hyaluronic acid
Silicone, liquid (1955)	polydimethylsiloxane, 350 centistokes viscosity, withdrawn 1976
Touchline	hyaluronic acid
Zyderm I (1975, marketing approval 1981)	bovine collagen + 0.3% lidocaine HCl: 35 mg/ml
Zyderm II (1983)	bovine collagen + 0.3% lidocaine HCl: 65 mg/ml
Zyplast (1985)	bovine collagen cross-linked with glutaraldehyde + 0.3% lidocaine HCl

Injectables are classified as "Medical Devices with the addition of an active medical substance."

Breast implant FILLER MATERIALS

• Dextran	
• Methylcellulose-hydrogel	Monobloc, Laboratoire Arion (with methylene blue)
• Polyacrylamide	Kiev, Italy
• Polysaccharide-hydrogel	
• Polyvinylpyrrolidone	Misty Gold, Novagold
• Povidone-iodine	
• Saline, serum physiologique	
• Seaweed	
• Silicone gel	McGhan, Mentor, Polytech-Silimed, Nagor, Eurosilicone, PIP, LPI, CUI, Lab. Sebbin, Lab. Arion
• Triglyceride (Trilucent)	Lipomatrix

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 of or compensation for an 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 in or on the human body by pharmacological, immunological or metabolic means but which may be assisted in its function by such means.

According to ISP 14630, an implantable device is a device intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye via surgical intervention which is intended to remain in place after the procedure. A medical device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for at least 30 days is also considered an implantable device. This application of biomaterial is not new either. In the 17th century, the subcutaneous implantation of mother-of-pearl or jade beads into the foreskin was described,[2] a practice remarkable enough for having succeeded at all at a time before the advent of asepsis and antibiotics. Piercings, therefore, are partially implanted devices and those penile implants totally implanted devices.

The practice of surgery has mainly been concerned with amputation, including the removal of tumors, for many centuries. Surgery then developed to include reconstructions and–in the latter part of the 19th century- to include transplantation surgery. Surgery has now entered a new phase—inductive surgery, i.e. the use of tissue engineering to induce the body to form a necessary replacement or desired enhancement.

Biomaterials have always been employed by surgeons. One has only to think of naturally present materials for suturing. Horsetail hairs, for instance, were still used for that purpose in the last decade of the 20th century in Eastern Europe. The introduction of biomaterials on a large scale only occurred with the advent of reconstruction, the surgical replacement of tissue. This was and is still done with transplants and implants.

How research and development of an implant evolves over the years can be well described, taking silicone breast implants (SBIs) as an example:

1930s	The polymer poly(dimethylsiloxane) was discovered; under the name silicone, it is an invention in search of an application.
1962	Gerow en Cronin (USA) manufactured an envelope or shell of silicone (silastic) with a semi-fluid or gel-like silicone content.
1964	Arion (France) developed saline-filled breast implants with a silicone shell. Implants have a smooth surface and Dacron patches for fixation inside the pocket into which they are inserted.
1975	Fixation patches discontinued.
1976	Double lumen implants with saline in the outer lumen to diminish diffusion or migration of small chain polymers through the shell, which caused constriction of the surrounding tissue scar.
1979	Eight companies worldwide manufactured and marketed SBIs. Companies were sold and bought by one another and by others.
1979	Thicker shells were manufactured to prevent gel diffusion.
1985	A reverse double lumen SBI was marketed; it had an inner chamber which could be filled with saline to the desired volume; it also had the advantage of slowing down gel diffusion.
1987	Silicone-gel filled SBIs with a textured surface instead of a smooth one, appeared on the market; tissue ingrowth into the surface diminished the occurrence of scar constriction.
1989	Saline-filled SBIs with textured surfaces were marketed.

1993	Highly cohesive gel-filled SBIs were manufactured; the semi-solid gel contained few short polymer chains and showed virtually no diffusion of silicone.
1994	Pear- or teardrop-shaped SBIs were marketed instead of the round ones.
1995	Triglyceride as an SBI-filler instead of silicone gel or saline was marketed. X-rays necessary for mammography could penetrate the implant and can show up cancer, in contrast to silicone gel or saline which blocked X-rays, making multiple radiographies necessary for examination; the manufacture of triglyceride-filled implants was ceased within a few years because of saponification by body fluids diffusing into the implants.
1996	Hydrogel (polysaccharide, cellulose) introduced as an SBI-filler, but not allowed in every country.
2000	There were still no more than 10 SBI manufacturers in the world.

The manufacturing process of any device involves a cycle: basic research-design-testing-manufacturing-marketing-application-follow-up clinical and basic research, etc. (Fig. 1). The cycle leads to a spiral of ever increasing quality of the product. One sees that this is explicitly true for SBIs.

It is interesting to observe that the increasing interest of health authorities parallel the R&D of SBIs.

1991	A USA manufacturer lost a multimillion dollar lawsuit because a patient blamed her rheumatoid arthritis on her SBIs.
1992	The US Food and Drug Administration (FDA) called for a voluntary moratorium on the sale of SBIs in January until "safety and efficacy" have been proven by the manufacturers.

Countries like Australia, Canada, France, Italy and Japan followed the FDA moratorium blindly. In the UK and The Netherlands, health authorities consulted the plastic surgeons and decided not to limit the sale of SBIs whatsoever. In April 1992 the FDA lifted the moratorium for cases of breast reconstruction after operation in cancer patients, but continues the ban for aesthetic purposes. The silicone-affaire is born.

1997 In Europe, France was the only country to continue to ban SBIs.
1998 The Europarliament receives petitions from "silicone-survivors" to ban SBIs in Europe. An impartial scientific panel in the USA reported that there is no evidence of auto-immune (or other) disease caused by SBIs.
1999 Similar reports appeared in the UK and The Netherlands, produced at the request of Health Ministries. The European Commission considered that SBIs are under the scope of Council Directive 93/42 EEC on Medical Devices (covering safety and CE-certification) of 1993; they confirmed that the liability of manufacturers was covered by Council Directive 85/374 EEC of 1985.
2000 UK issued an alert on hydrogel filled implants.
2001 France lifted the ban on SBIs. The Europarliament voted against a ban on SBIs and sent its decision to the Commission and the Council of Ministers. Member States of the EU were requested to have registries of patients and SBIs.
2005 The Dutch Ministry of Health had still not taken any steps to set up a database for registering patients and SBIs.

The profession, i.e. medical doctors are taking care of post marketing surveillance (PMS) for a large part.[4] PMS concerns:

(1) Reporting adverse events and side effects
(2) Retrieval and analysis of explants
(3) Tracing and tracking of patients and implants, for which registries are indispensable. In the case of SBIs, an international registry has been set up.[3]

In general, however, medical doctors receive little information on biomaterials during their training. They are readily accustomed to the suture materials and implants used by their teachers. When they are approached by distributors who want to introduce new materials, doctors are pretty credulous and only a few study the literature on the chemical composition of the new material. Nor do they ask which notified body issued a CE-mark. Many lend credence and confidence to the simple assertion "FDA-approved." As we all know, the FDA is more of a political body than an ISO and a CEN, which institutions heavily rely for scientific input. Take an injectible like Biogel, consisting of poly(acrylamide). It is virtually impossible to produce a 100% pure polymer and there will always be traces of the extremely toxic monomer, mono(acrylamide). Few doctors know this and even fewer question the purity of the materials as advertised by the distributors.

Hospitals have become conscious of this and do not allow its doctors to give patients medicines that have not passed through thorough screening by hospital officials. The same goes for implants. Thus, doctors are rendered help in scrutinizing new biomaterials and patients are protected from doctors implanting devices that they carry to the hospital in their pockets.

Despite all these precautionary measures, catastrophes still occur. In the case of the silicone-affair, examples are the triglyceride- and the dextran-filled breast implants. Both triglyceride and dextran are regularly given to patients intravenously and many believed that filling a breast implant with them, would be innocuous. The contrary appeared to be true. Dextran attracted water through the porous silicone implant shell and patients asked their surgeon a few weeks after the implantation when their breasts would stop growing. Triglyceride attracts proteins and other chemicals from the body fluids, resulting in saponification and production of oxygen radicals. Thousands of Trilucent (triglyceride-filled SBIs) have been implanted all over the world. It is now recommended that all triglyceride-filled breast implants be explanted.

Medical doctors need to be educated in medical product development in order to understand device-related complications (infection, bio-incompatibility, dislocation, etc.)

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It was the reaction to the FDA's moratorium on silicone-gelfilled breast implants, that led people to not only look for other filling materials, but to make a profit by selling them, however experimental the material. The inadvertent vacuum caused by the unscientific (and rather political) FDA moratorium therefore caused many patients distress and worse.

In the case where a doctor is credulous, one cannot expect the patient to be distrustful or be suspicious of a new material. For example, even today male-to-female transsexuals have their hips enlarged with large amounts of fluid silicone injections, in which case the material slides through tissue planes all the way down to the ankle, causing painful swellings that are very difficult to treat, if at all.[1] There are still patients who have the girth of their penises enlarged with paraffin injections, resulting in granulomatous reactions that can only be removed by excision. Needless to say, the licences of the doctors performing such unethical practices should be suspended. Patients, on the other hand, need to be better informed, more critical and more aware of the danger of consulting "cowboys" in malafide private clinics with all the ensuing complications.

Doctors have become more critical and are increasingly involved in post-marketing surveillance: IQUAM[4] and IBIR[2] are proofs of that.

The near future will undoubtedly see tissue engineering (TE) blooming. The TE constructs consist of a scaffold of degradable biomaterials serving as a matrix on which autologous cells cultured for multiplication are sown. Growth factors may be added to increase the potential of the entire construct. On the one hand, TE will offer more possibilities for treating patients; on the other, they are expected to increasingly replace implants. The future is bright; the future is inductive surgery.

This book contains two parts. Part I describes the more fundamental aspects of biomaterials research, such as cell-material interactions, inflammatory responses, animal models for biomaterials research and technology assessment. Part II describes various clinical applications of biomaterials: a state-of-the-art, its limitations and an overview of the problems that still have to be solved. For each application, the anatomy and morphology of the location where the implant becomes positioned is briefly described.

References

1. Hofer SOP, Damen A, Nicolai JPA. (2000) Large volume liquid silicone injection in the upper thighs: a never ending story. *Eur J Plastic Surg* **23**(4):241–4.
2. Teensma BN, Nicolai J-PA. (1991) Literaire filologische en moralistische bespiegelingen over de Siamese penisbel. *Bijdragen tot de Taal-*, *Land- en Volkenkunde (BKI)* **147**(1):128–39.
3. www.ibir.org
4. www.iquam.org

Abbreviations

CE: Conformité Européenne
CEN: Comité Européen de Normalisation
FDA: Food and Drug Administration
ISO: International Standards Organisation
PMS: Post Marketing Surveillance
R&D: Research and Development
SBI: Silicone Breast Implants