

# 1 Biomedical Instrumentation and Devices



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## 1.1 Classification of Biomedical Instruments and Devices

Worldwide the medical instrumentation and device industry is worth more than 100 billion US dollars annually. A number of multinational companies, including Boston Scientific, Medtronic, Abbot Medical Devices, Johnson & Johnson and Novo Nordisk, have a major focus on the development, sales and distribution of several broad classes of medical devices. In the United States, the five largest areas of medical device revenue are orthopaedics, ophthalmology, cardiology, audiology and surgery, each with revenues of about 20 billion US dollars.

**Table 1.1** Device classification panels: upper tier ([www.fda.gov/MedicalDevices/DeviceRegulationandGuidance](http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance))

Medical specialty	Regulation citation	Medical specialty	Regulation citation
Anaesthesiology	Part 868	Microbiology	Part 866
Cardiovascular	Part 870	Neurology	Part 882
Chemistry	Part 862	Obstetrical and gynaecological	Part 884
Dental	Part 872	Ophthalmic	Part 886
Ear, nose and throat	Part 874	Orthopaedic	Part 888
Gastroenterology and urology	Part 876	Pathology	Part 864
General and plastic surgery	Part 878	Physical medicine	Part 890
General hospital	Part 880	Radiology	Part 892
Haematology	Part 864	Toxicology	Part 862
Immunology	Part 866		

Hundreds of smaller companies, including new start-ups, concentrate on more specialized parts of the market. A search of the US-based Food and Drug Administration (FDA) Code of Federal Regulations (CFR) in 2014 showed that over 1700 distinct types of (bio)medical devices and instruments are listed. The FDA defines a medical device as:

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is [...] 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, or 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 intended 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.

Medical devices are classified in many tiers and sub-tiers. Table 1.1 shows the upper classification tier, which is based on medical specialty.

The next level of classification is illustrated in Table 1.2 using Part 870 on cardiovascular devices as an example. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. Class I devices have the lowest risk, Class II intermediate risk and Class III are those with the highest risk. Devices for the European market have similar classes. The class of the medical device determines the type of premarketing submission/application required for regulatory approval: this process is considered in more detail in section 1.3. Each of the elements in Table 1.2 has a small section that describes in very general terms what the device does and its classification in terms of performance standards. As an example:

### 3 1.2 Outline of the Design Process: From Concept to Clinical Device

**Table 1.2** Device classification panels: Subpart B cardiovascular diagnostic devices

Device	Section	Device	Section
Arrhythmia detector and alarm (including ST-segment measurement and alarm)	870.1025	Catheter guide wire	870.1330
Blood pressure alarm	870.1100	Catheter introducer	870.1340
Blood pressure computer	870.1110	Catheter balloon repair kit	870.1350
Blood pressure cuff	870.1120	Trace microsphere	870.1360
Non-invasive blood pressure measurement system	870.1130	Catheter tip occluder	870.1370
Venous blood pressure manometer	870.1140	Catheter stylet	870.1380
Diagnostic intravascular catheter	870.1200	Trocar	870.1390
Continuous flush catheter	870.1210	Programmable diagnostic computer	870.1425
Electrode recording catheter or electrode recording probe	870.1220	Single-function, preprogrammed diagnostic computer	870.1435
Fibreoptic oximeter catheter	870.1230	Densitometer	870.1450
Flow-directed catheter	870.1240	Angiographic injector and syringe	870.1650
Percutaneous catheter	870.1250	Indicator injector	870.1660
Intracavitary phonocatheter system	870.1270	Syringe actuator for an injector	870.1670
Steerable catheter	870.1280	External programmable pacemaker pulse generator	870.1750
Steerable catheter control system	870.1290	Withdrawal-infusion pump	870.1800
Catheter cannula	870.1300	Stethoscope	870.1875
Vessel dilator for percutaneous catheterization	870.1310	Thermodilution probe	870.1915

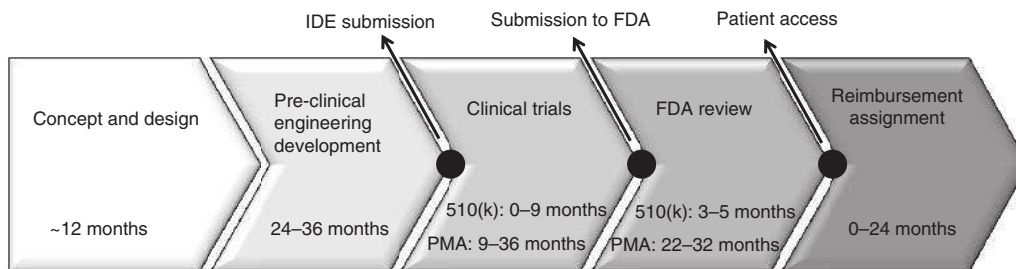
Sec. 870.1130 Non-invasive blood pressure measurement system.

- (a) Identification. A non-invasive blood pressure measurement system is a device that provides a signal from which systolic, diastolic, mean, or any combination of the three pressures can be derived through the use of transducers placed on the surface of the body.
- (b) Classification. Class II (performance standards).

## 1.2 Outline of the Design Process: From Concept to Clinical Device

Figure 1.1 gives a schematic of the process of producing a new medical instrument or device. Each of the steps is discussed briefly in the next sections, with the exception of reimbursement assignment, which although an obviously important topic, varies widely by country and political philosophy. With the ever-increasing costs of healthcare there is a strong recent trend towards what is termed ‘**value-based**’ medicine, i.e. recognizing that there is a trade-off between improved

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**Figure 1.1** General outline of the steps involved in the design, engineering and safety testing, submission process and, ultimately, financial planning for a new medical instrument or device.

healthcare and its availability to the public due to the associated increased costs. Overall, the aim is high-quality care at an affordable cost. As an example of why value-based medicine has become an important concept, consider that the share of the total economy of the United States taken up by healthcare has more than doubled since the 1970s, with a total budget of over 20% of gross domestic product in 2016. However, a recent report stated that the “USA stands out for not getting good value for its healthcare dollars”. In the past, new products (both medical drugs and devices) were designed, approved and integrated into medical care even if their costs far outweighed slight improvements in performance and clinical diagnosis. The new paradigm is to calculate the ‘value’ of a new product, with value defined as the degree of improvement relative to its increased cost (which also includes associated costs in terms of parameters such as the need for highly trained operators and additional training). The implication of this new approach is that medical device manufacturers should aim new products at healthcare areas that are outliers in terms of their low cost-effectiveness, and so can be improved the most, rather than on incremental increases in the performance of devices that already provide good value for money.

### 1.2.1 Engineering Design

One of the most common comments about the role of engineering in medicine is that engineers are very good at discovering a new concept or technology, and then try desperately to find a clinical application for this technology! This approach, of course, runs counter to every fundamental concept in design engineering: first define the problem and the goal, and *then* design the solution. During the invention phase, it is critically important to have an appreciation of the anatomy and disease pathophysiology.

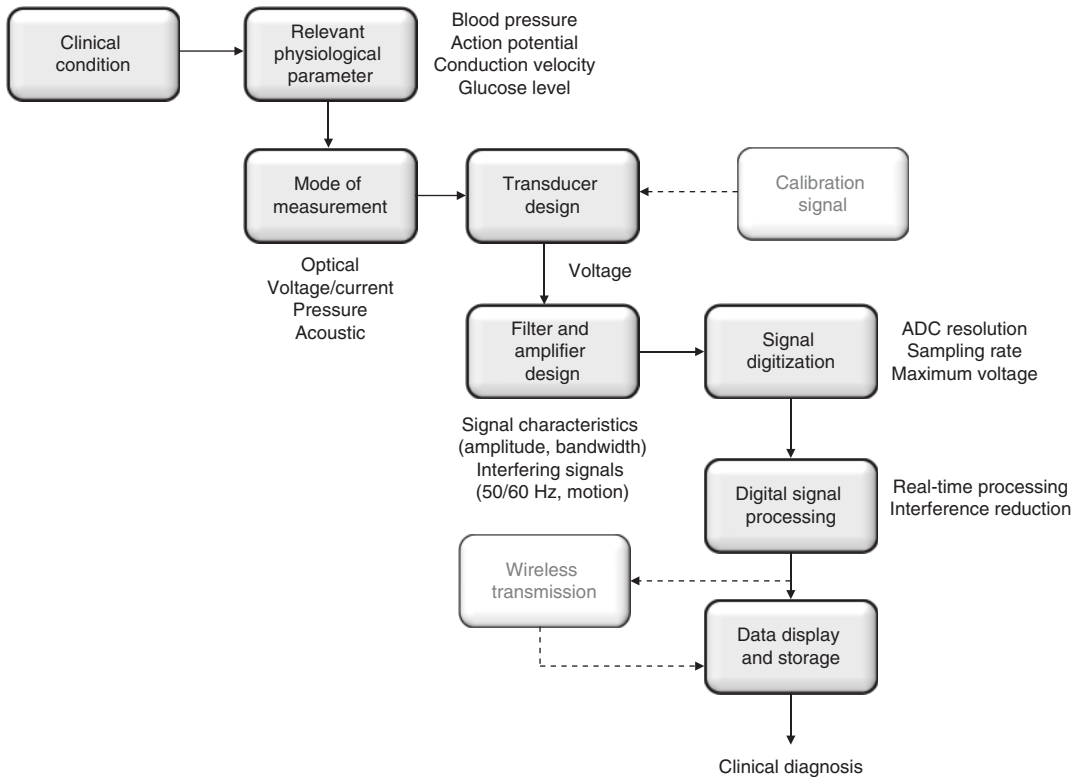


Figure 1.2

Generalized block diagram of the individual modules of a biomedical instrument. Grey text and dotted lines represent features that are only present in certain instruments.

Figure 1.2 shows a general block diagram of the individual components of a biomedical instrument, with examples of different measurements, sensors, filters and data acquisition systems. Often the desired measurement is based inside the body, but ideally the measurement is non-invasive where possible: this means that the signal has to be measured indirectly. How can this signal be measured with the highest fidelity? This involves removing interfering signals from external sources, including other physiological processes such as motion, which may produce signals many times larger than the ones we are trying to measure. Many of the biosignals have a very low magnitude: biopotentials are in the microvolt (electroencephalography) to millivolt (electrocardiography) range, internal pressures are on the orders of kilopascals (blood pressure sensors) and biocurrents lie in the microamp to milliamp range (glucose sensors). The frequencies of the biosignals are also rather low, generally in the range DC to hundreds of hertz (although acoustic signals for hearing aids are in the DC–16 kHz range), meaning that the hardware can be designed for low-frequency filtering and amplification (operational amplifiers).

However, when implanted sensors are needed, power and signal transmission through the body requires much higher frequencies (typically around 400 MHz) and so high-frequency circuits must be integrated into these types of devices.

As an example of the general concepts involved in medical instrumentation design, consider one of the most commonly used machines in a hospital, the electrocardiogram (ECG). This instrument measures how healthy the heart is in terms of its fundamental purpose of pumping blood around the body. The pumping action is caused by action potentials occurring in the pacemaker node of the heart and this electrical activity spreading throughout the heart with well-defined spatial and temporal characteristics, in turn causing the heart as a whole to expand and contract to produce the desired pumping function.

Different pathophysiologies of the heart cause different problems with the conduction path of the action potentials through the heart (**clinical condition**). The fundamental measurements that reflect physiological changes are the action potentials in different areas of the heart (**relevant physiological parameter**). However, the measurement must be performed outside of the body. By analyzing the propagation of ionic currents, produced by the action potentials, through the body, electrical activity in the heart can be detected indirectly on the surface of the body using a number of electrodes placed at different locations (**mode of measurement**). These electrodes transform/transduce the ionic currents into an electrical voltage (**transducer design**). In addition to the desired ECG voltage, there are many electrical interference signals that are also detected by the electrodes, and these interferences can be filtered out knowing the respective frequency ranges over which the ECG signals and interference signals occur (**filter design**). In order to digitize the filtered ECG signal with a high degree of accuracy, signal amplification is needed to use the full dynamic range of the analogue-to-digital converter (**amplifier design, signal digitization**). After digitization, further filtering of the signal can be performed using very sharp digital filters to remove artefacts such as baseline wander or any remaining 50/60 Hz noise (**digital signal processing**). Finally, by analyzing the shape and general characteristics of the ECG voltage waveform in each of the electrodes (**data display**), it is possible to detect abnormalities and to trace these abnormalities back to specific malfunctions of the heart.

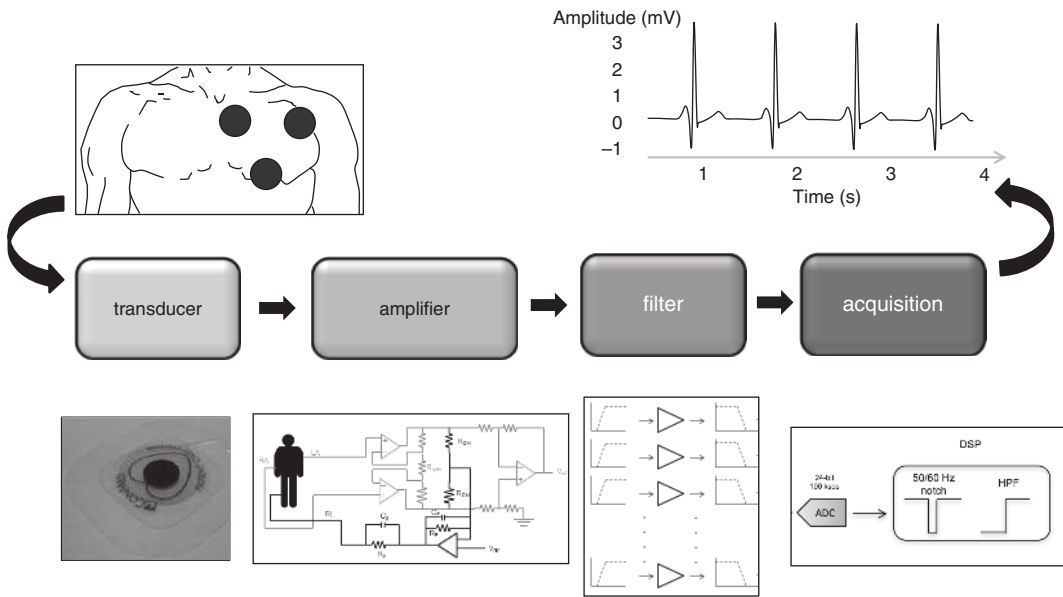
Table 1.3 outlines the characteristics of the ECG signal, as well as those of different interference signals, which can actually have a much higher amplitude than the ECG signal itself.

Figure 1.3 shows a block diagram of the individual components of the ECG data acquisition system, which are covered in much more detail in Chapter 5.

Figure 1.4 shows an example of a condition, atrial fibrillation, which produces a clear alteration in the ECG signal. Atrial fibrillation can be caused by

**Table 1.3** Design criteria for the electrocardiograph

Physiological metric	Cardiac action potential (voltage)
Indirect measurement device	Electrode (placed on the skin)
Mode of action	Converts ionic current into a voltage
Size of detected signal	1–10 mV
Frequency of detected signal	1–50 Hz
Interfering signals	Electrode half-cell potential; coupling to power lines; breathing; muscle motion; blood flow
Size of interfering signals	1.5 V (power lines); 300 mV (half-cell potential); ~mV (muscle motion)
Frequency of interfering signals	50/60 Hz (power lines); DC (half-cell potential); ~10–50 Hz (muscle motion); ~0.5 Hz (breathing)
Required time resolution	One measurement every 200 ms
Required accuracy	±1 mV
Required dynamic range	0–100 mV

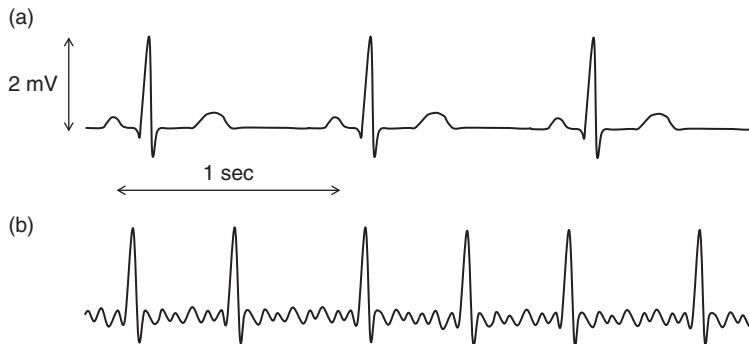


**Figure 1.3** Block diagram of the different modules used in detecting the ECG signal.

a number of different conditions including heart failure, coronary artery disease, disease of the heart valves, diabetes and hypertension. Although the waveform shown in Figure 1.4 is highly characteristic of atrial fibrillation, the final diagnosis of the particular condition is usually made by combining the ECG with other diagnostic techniques such as ultrasound and computed tomography.

**Figure 1.4**

(a) Example of a normal ECG signal in a healthy person. (b) Example of atrial fibrillation.



### 1.3 Regulation of Biomedical Instrumentation and Devices

Regulatory bodies such as the FDA and European Commission (EC) do not set specific regulations per se, but rather rely on standards that are produced by working groups such as the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC), as well as country-specific organizations such as the American National Standards Institute (ANSI) and the European Committee for Standardization (CEN).

Initially, a company in the United States has to make a best-guess selection of the appropriate class (I, II or III) of their device. Class I devices do not need to undergo clinical trials or biocompatibility tests, since by the Class I definition there is sufficient evidence of safe operation based on similar devices already on the market. There are still some requirements, such as adhering to the FDA's quality systems regulation (QSR), which represents guidelines for safe design and manufacturing. Class II devices are usually taken to market via the 510(k) process. The particular medical device must be shown to be substantially equivalent to an existing design, so that the FDA can compare it. Equivalence can usually be assessed using bench tests and animal testing without the need for human trials: only about 10% of annual 510(k) submissions require clinical data. A second route for Class II devices is the de novo 510(k) path, which is for devices that do not have the risks associated with Class III devices, but for which no substantial prior information exists or similar devices are not yet on the market. These require a higher level of proof of efficiency than the standard 510(k) but less than for the pre-market approval (PMA) required for Class III devices. The 510(k) submissions are standardly reviewed on the timescale of a few months, but the amount of paperwork is substantial, running to several hundreds of pages. Class III devices require PMA regulatory approval, and represent devices that have the highest potential risk to patients or have significantly different technology than those that



already exist in the target application field. Typically, large multi-centre randomized clinical trials are required for these types of devices. If a device, such as a coronary stent, is defined to be ‘life-sustaining’, then this type of Class III device requires a PMA, even though the new stent may be very similar to those already on the market [1].

One obvious question is how can one actually perform clinical trials on devices that are only officially approved after a successful clinical trial? This process requires an investigational device exemption (IDE), which represents official permission to begin such a trial. For low-risk devices, the local institutional review board or medical ethics committee at the hospital or laboratory where testing is to be performed, can give such approval. For devices that ultimately will require a PMA, clearance must be given by the FDA. The IDE does not allow a company to market the device, merely to perform the clinical trials required to obtain a PMA. However, in the United States companies can charge for investigational devices. The requirements for receiving an IDE are usually extensive biological and animal testing (covered in detail in Chapter 9).

The description above refers explicitly to the situation in the United States, but there are broadly equivalent regulatory standards in the European Union (EU), with some important differences [2, 3]. There are three different European directives: (i) implantable devices are regulated under directive 90/385/EC; (ii) most other devices are regulated under directive 93/42/EC; and (iii) in vitro diagnostic devices (i.e. used on substances produced by the body) are regulated under 98/79/EC [4]. In the EU, every marketed medical device must carry a *Conformité Européenne* (CE) mark indicating that it conforms to relevant directives set forth in the EC Medical Device Directives. A device with a CE mark can be marketed in any EU member state. Devices are classified as low risk (Class I), moderate risk (Classes IIa and IIb) and high risk (Class III). Medical devices that are non-implantable and considered low risk are ‘self-marked’, meaning that the manufacturer itself simply certifies compliance and applies a CE mark. High-risk devices must undergo a more extensive outside review by a ‘Notified Body’ (NB) within that country, which is authorized by that country’s Competent Authority, or health agency, to assess and assure conformity with requirements of the relevant EC directive. One of the fundamental differences between the regulatory systems in the United States and Europe is that before approval can be granted for a medical device in the United States, it must not only be shown to be safe, but efficacious. In contrast, medical devices approved in Europe need only demonstrate safety and performance, i.e. they perform as designed and that potential benefits outweigh potential risks: they are not required to demonstrate clinical efficacy.

## 1.4 Safety of Biomedical Instrumentation and Devices

The safety of a biomedical instrument or device refers to three different facets of the equipment: the hardware, the software and the user interface. The general principles are that in hardware, two *independent failures* should not harm the patient; software is designed such that the chances of harm arising from *inevitable* bugs are acceptably low; and the design of the user interface concentrates on making the man–machine interface as safe as possible. The increasing use of mobile health (m-health) applications has resulted in new FDA guidelines. The FDA has defined a mobile app to constitute a medical device ‘if a mobile app is intended for use in performing a medical function (i.e. for diagnosis of disease or other conditions, or the cure, mitigation, treatment, or prevention of disease), it is a medical device, regardless of the platform on which it is run’. Mobile health technology is classified into Classes I, II or III in the same way as physical medical devices. For example, a mobile app that controls a glucose monitor, and stores and transmits the data wirelessly to the physician, is subject to exactly the same regulations as the glucose monitor itself.

Despite all of the safety requirements in place, it is estimated that roughly 1.5% of 501(k) predicate devices have to be recalled. There are also several instances of major recalls involving tens or hundreds of patient deaths (see Problems).

### 1.4.1 ISO and IEC Standards

As mentioned earlier, regulatory bodies do not design specific safety tests that medical devices must pass, but instead rely on standards that have been devised by independent testing agencies. For example, ISO 14971:2007 specifies the procedure by which medical device manufacturers can identify potential hazards in order to estimate and evaluate the associated risks. Methods must be provided to control these risks, and to monitor the effectiveness of the control methods. Figure 1.5 shows a schematic of the methods for categorizing risks [5].

Provided below is a brief summary of key elements of ISO 14971:2007 with sections in *italics* (not present in the original document) outlining the essential concepts.

The requirements contained in this International Standard provide manufacturers with a framework within which *experience, insight and judgment* are applied systematically to manage the risks associated with the use of medical devices. This International Standard was developed specifically for medical device/system manufacturers using established principles of risk management [ . . . ] This International Standard deals with processes for *managing*