Chapter 13
Ethical Aspects in Medical Devices and Ethical Committees in Clinical Trials and Regulations

Sergio Cerutti

Abstract Ethical problems are indeed relevant when dealing with medical devices, apparatuses and systems. The fundamental aspect of such devices is that they are employed for making diagnosis, therapy and rehabilitations on human subjects and therefore they manifest results in a very important field of applicative science, with direct cultural, economic, social implications and fallouts. In addition to that, it is often the case that these pieces of equipment are directly connected to the patient in various and different experimental conditions, thus creating dangerous potential situations for the patient and her/his environment conditions (macroshocks and microshocks). The role of safety and performance standards are therefore critical in order to maintain a correct and proper use of these technologies and avoiding the generation of risks and hazards for patient's health. Therefore, the "virtuous" challenge that has to be won by scientists and operators in this field is to be able to implement a system with reliable laws and rules, clear and complete technical standards, well trained clinical and technical personnel. Finally, ethical issues involve many different cultural, clinical, and managemental aspects, not necessarily confined within the concepts of modern biomedical technologies, which are of great importance and interest and which are often underestimated.

Introduction

A basic point to be remarked is that the compartments of pharmaceutical drugs (PHD) and medical devices (MD) are actually strictly regulated.

Just to provide an idea of the real impact of these compartments, it is worth to mention that the total world PHD expenditures (2019) has been of about 1200 billion US $ (about 15% of the total expenses for Health [35% USA and Canada, 28% Europe, 26% Asia, etc.], while the expenses for Medical Devices have been around 520 billion US $ [44% USA e Canada, 29% Europa, 20 Asia, etc.].

S. Cerutti (✉)
Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milano, Italy
e-mail: sergio.cerutti@polimi.it

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Conversely, the number of patents for MD has had a strong increasing in the last years and reached the quote of 60,000, compared to a modest increment in the area of PHDs. Therefore, strong developments are foreseen in the future for the MD compartment in respect to PHD compartment, at least for the next expected years.

The present chapter describes the Ethical Issues with the current Regulations, in particular referring to the MD compartment. As it is well known, on 2017, the new Regulation on MD's replaced the Directive on the same topic: a 3-year term was granted for a gradual adaptation to the new document and another year was given for the 2019–2021 epidemy. Therefore, the deadline for a mandatory application of it has been fixed on May 26th, 2021. Analogously, the deadline for a mandatory application of in vitro Diagnostics Regulation (IVDR) has been fixed for May 26th, 2022. As for a coherent choice from the Author of this section, the Italian situation is mainly analysed: it is obviously inserted into the frame of EU legislation and relevant Regulations. Therefore, while some considerations will be referred to the Italian situation only, most of the rules do have a clear European perspective. These aspects will be clarified within the text.

13.1 Clinical Trials for Medicinal Products (Pharmaceutical Drugs)

The fundamental *ethical principles* to which the studies on clinical trials referred to PHD must conform, have an origin from Helsinki declaration [1], Oviedo Convention [2], Guidelines of EMA for Clinical Trials [3] and from the requirements of the international standards of **Good Laboratory Practice (GLP)**, **Good Clinical Practice (GCP)** guidelines and **Good Manufacturing Practice (GMP)** guidelines [4]. These rules and prescriptions constitute fundamental tools for implementing that process which incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of **clinical research involving the participation of human subjects** and aims at maintaining data or goods resulting from such a scientific research, in general, at a high level of quality standards.

Good laboratory practice (**GLP**) is intended to ensure the trustworthiness of laboratory data and regulates the processes and conditions under which clinical and non-clinical research is conducted. GLP also governs how these research facilities should be maintained [Directives 79/831 CE, 99/11 CE and 99/12 CE] [5]. Good clinical practice (**GCP**) guidelines are instead dictated by the International Conference on Harmonization (**ICH**). The ICH GCP governs the ethical and scientific quality of *clinical trials.* Hence, the ICH GCP covers topics such as the study design, methodology, and data reporting related to clinical trials [ICH E6 (R2) Good clinical practice] [6]. Finally, **GMP** regulates the design, monitoring, and control of manufacturing processes and facilities. GMP compliance, for example, ensures the identity, strength, quality, and purity of PHD products and it is designed to minimise the risks involved in any pharmaceutical production that cannot be eliminated

through testing the final product (Regulation No. 1252/2014 and Directive 03/94/EC, applying to active substances and medicines for human use, World Health Organization) [7].

The European Medicines Agency (EMA) relies on the results of clinical trials carried out by pharmaceutical companies to reach its opinions on the authorisation of medicines. Although the authorisation of clinical trials occurs at Member State level, the Agency plays a key role in ensuring that the standards of good clinical practice (GCP) are applied across the European Economic Area (EEA) in cooperation with the Member States. It also manages a database of clinical trials carried out in the European Union.

GMP Standards have been adopted by European Union (EU) and acknowledged inside national regulations. In particular, Directive 2001/20/EU of the European Parliament on the approximation of the laws, regulations and administrative provisions of the Member States is related to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use. Further, Directive 2005/28/EC deals with the Good Clinical Practice, regarding how to conduct clinical trials of medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

Another Directive (2001/83/EU and successive updates) is relative to a Codex concerning PHD for human use, while Directive 2003/94/EU concerns Good Manufacturer Practice relative to PHDs for human use as well as to experimental PHDs for human use. Finally, Regulations EU 536/2014 deal with Clinical Trials in Humans and have been finally recognised with updates on 16/12/2014.

The above-mentioned Directive 2001/20/EU defines as "clinical trial" "any study on humans with the aim to discover or verify clinical, pharmacological or other pharmacodynamical effects of one or more experimental PHDs and/or to single out any adverse reaction to one or more experimental PHDs, and/or to study their assimilation, distribution, metabolism and wash-out, with the purpose to verify the safety and/or performance, as well as other elements of scientific character or not". This definition includes clinical trials carried on in one or more centres in Europe (clause 2, comma 1, letter a). Such trials are defined "*interventional*", in respect to "*observational*". Figure 13.1 illustrates the very long procedure which stays behind an approval of a new pharmaceutical drug.

The steps to be fulfilled are:

Pre-Clinical Test (around 3 years duration): Such a duration is estimated after a preliminary and initial period of testing new molecules, compounds or other chemical substances (around 3–3.5 years duration). That is about 6.5 years in total, as indicated in the first block of Fig. 13.1.

Such tests must evaluate the safety of the active principle (toxicity), its behaviour after the administration, in terms of absorption, distribution, metabolism, elimination (ADME) and pharmacokinetics (PK). During this phase, the drug is produced on pilot scale, respecting Good Laboratory Practice (GLP) Standards.

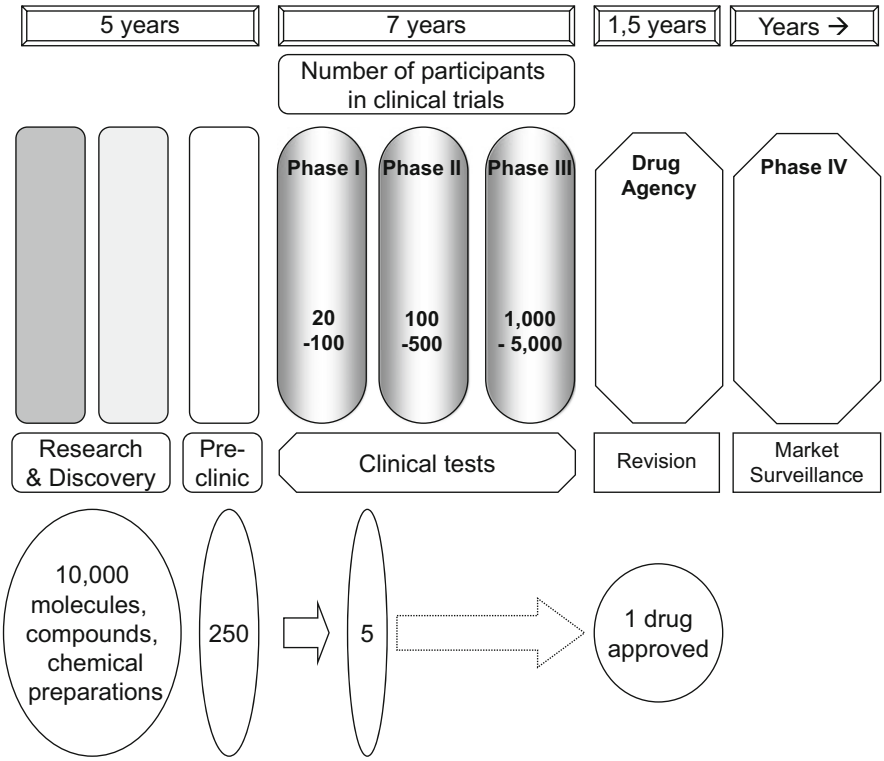

Fig. 13.1 The articulated, complex and very long procedure for the registration of a new pharmaceutical drug at EMA (European Medicines Agency)

Clinical Trials (7 Years)

The second block depicts the so-called *Clinical Trials* and are usually carried out in three main phases (Phase I, II, III). Every phase approaches different aspects and the outcome of every study phase is important to decide whether the experimentation of the new drug in a determined phase could proceed to the successive one. It is necessary to check the different phases of clinical development in order to guarantee the safety and rights of the people involved into the clinical studies, the data reliability and the compliance with the GCP Standards.

Phase I

Phase I studies are dedicated to the analysis of the **safety and tolerability profiles** of the product and generally are carried out on human healthy volunteers. The decision to pass to Phase II is taken in consideration of the obtained results in Phase I, during which sufficient information shall be collected on pharmacokinetics and in which the drug must have demonstrated to have reached a good safety and tolerability levels.

Phase II

During Phase II, the drug is given to a selected group of patients (generally 100–300 people). The aim of these studies is to determine whether the new drug is really **effective for the treatment** of the pathology. Further, the dose and frequency of delivery must be determined to obtain the better efficacy with the lower possible number of adverse events. At the end of Phase II, the efficacy data obtained, the safety profile and adverse events must be examined and properly considered at the aim of deciding whether the drug could pass on to Phase III of clinical trials and to process the best design for the successive studies.

Phase III

Phase III studies are programmed to confirm the **drug efficacy and to monitor the adverse events over longer time span**: in fact, they base on the observation of a greater number of patients (around 1000–3000 patients of different geographic areas) and for a longer period of time (in average 2–3 years, depending upon the type of therapy and pathology. Once Phase III studies are completed and if the results have been significantly confirmed, proper documentation on drug efficacy and safety is sent to regulatory Authorities in order to receive the "Authorisation to the Market Admission (AMA)".

Approval of Regulatory Authority and Marketing (1–2 Years)

The approval of a drug from a regulatory Authority is often a rather long process which requires about 1 year for the revision of all the documentation and the delivery of a final decision. After the Authorisation to the Market Admission (AMA), the following step is to launch the product into the market, involving marketing departments which must produce a detailed market study, a communication plan, a registered mark and a suitable training plan for the personnel who will manage the product promotion.

Post-market Surveillance (Phase IV)

After the drug is approved by the regulatory authorities, it is necessary to execute the so-called **pharmaco-vigilance**, i.e. to continue to monitor the safety, by collecting information about drug **adverse reactions** from different sources, including spontaneous warnings. Such an activity is a law requirement and is fundamental to guarantee public health, as it is fundamental to confirm the safety data collected during clinical trials on the real patient's population and over a long term. Among the pharmaco-vigilance activities there is the continuous monitoring of risk/benefit ratio in order to guarantee that the advantages of the therapy with the product are always greater than the risks originated from possible side effects.

It is worth to remark the fact that generally the whole procedure starts with the analysis of a huge number (even *10,000*) of initial molecules or compounds and finishes (hopefully) with the official approval of *one* drug! And that happens 15 years after the first step, if no emergential procedure is decided to be put into practice!

Observational Studies on Drugs

As illustrated by AIFA, the Italian Agency for Drugs, inside the Guidelines for Observational Studies on Drugs, it is established that the observational studies on drugs are particularly important for the evaluation of the safety profile in the normal use conditions and over a great number of patients, to go deep into the efficacy of the clinical practice, the pertinency of the prescriptions and the evaluations of "pharma-economic type". A statement of that kind is also present in other European legislations and therefore it is here presented as an example of a more general case.

Due to their characteristics, observational studies do not imply additional risks to the patients to whom the best conditions of clinical assistance are offered. Consequently, they require differentiated procedures in respect to what is required in the experimental clinical studies.

Particular caution is required in order to avoid that a clinical trial is presented as an observational study.

To this purpose, it is important to note that drug studies must satisfy the following conditions in order to be considered non-experimental:

1. The drug must be provisioned according to the use indications, as in the Authorisation to the Market Admission in Italy (or in another European Country).
2. The prescription of the drug must be part of the clinical practice.
3. The decision to prescribe a drug to the single patient must be independent from the one to include the patient in the study.
4. Diagnostic and valutative procedures must comply with the current clinical practice.

It is necessary that Ethical Committees are informed on the development of these studies in the health structure or on their territorial jurisdiction. It is also necessary that, according to the proposed observational study, Ethical Committees always receive a notice of the study or a formal request for the formulation of an opinion.

13.2 Clinical Trials on Medical Devices and In Vitro Diagnostics Medical Devices

Actually (2021), the entire sections of MD and IVD-MD are under the umbrella of two Regulations, which have the force of laws in Europe. One on MD and the other one on IVD-MD (see also Fig. 13.2).

On May 2021, the EU MDR has replaced the EU's current Medical Device Directive (93/42/EEC) and Directive on Active Implantable Medical Devices (90/385/EEC). On May 2022 the EU IVD-MD—Regulations will replace the EU current in vitro Diagnostic Medical Devices Directive (98/79/EEC).

These two new Regulations were adopted on 5 April 2017, and they entered into force on 25 May 2017. These have replaced the existing Directives, as indicated.

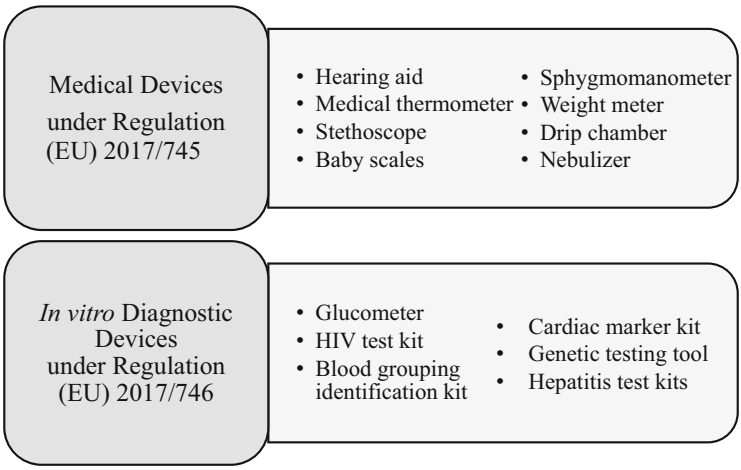

Fig. 13.2 Examples of equipment covered by the two Regulations on Medical Devices (MDR) and in vitro Diagnostics Medical Devices (IVD-MD)

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on **medical devices**, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on **in vitro diagnostic medical devices** and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

The new rules will only apply after a transitional period. Namely, 3 years after entry into force for the Regulation on medical devices (**Spring 2020)** and later on postponed to **2021** for the COVID epidemy) and 5 years after entry into force (**Spring 2022**) for the Regulation on in vitro diagnostic medical devices.

The need for a re-formulation of these **Regulations** came from serious incidents connected to deficits in medical devices (*silicon-gel mammary prostheses, metal-to-metal hip prostheses, etc.*) happened in the last decades and which influenced a lot even European public opinion. The former legislation, based upon **Directives**, demonstrated to be unable to avoid these incidents. This underlines the importance of the ethical issue about the full compliance to all safety and risk requirements.

13.2.1 The New Regulations on MD in a Nutshell

The new Regulations contain a series of extremely important improvements to modernise the current system. Among them are:

- **stricter ex-ante control for high-risk devices** via a new pre-market scrutiny mechanism with the involvement of a pool of experts at EU level

- the **reinforcement of the criteria for designation and processes for oversight of Notified Bodies**
- **the inclusion of certain aesthetic devices** which present the same characteristics and risk profile as analogous medical devices under the scope of these Regulations
- the introduction of a **new risk classification system for in vitro diagnostic medical devices** in line with international guidance
- **improved transparency** through the establishment of a comprehensive EU database on medical devices and of a device traceability system based on Unique Device Identification
- the **introduction of an "implant card"** containing information about implanted medical devices for a patient
- the **reinforcement of the rules on clinical evidence**, including an EU-wide coordinated procedure for authorisation of multi-centre clinical investigations
- the **strengthening of post-market surveillance** requirements for manufacturers
- **improved coordination mechanisms** between EU countries in the fields of vigilance and market surveillance

The stages of CE mark procedure for Medical Devices are:

1. Device classification
2. Compliance check of General Safety and Performance Requirements (SPRs)
3. Delivery of CE Mark of the product

For a detailed analysis of the basic philosophy, the definitions and international Regulations for Medical Devices and in vitro Diagnostics Medical Devices, see Chap. 4 of this book.

1. The *Classification* is the first action which has to be made by the manufacturer in order to single out the device class and to adopt the relevant mark procedures.
2. Any medical device must comply with the so-called General Safety and Performance Requirements (GSPRs'). These requirements, which are indicated in the EU Regulations, are mandatory for both the device and its production system. The objective is that the devices must be designed and produced in such a way that their use does not threaten patient's clinical state, nor user's or third party's safety and health, when they are used under the conditions and for the expected aims. The possible risks must be at an acceptable level, taking into account the benefits brought to the patient and being compatible with a high level of health and safety protection. That means that, in order to produce a medical device, the manufacturer must demonstrate that not only its product, but also the manufacturing process in its different aspects are in agreement with these requirements (project, fabrication, controls, etc.).

Compliance with the 'General Safety and Performance Requirements (GSPRs)' is a cornerstone in establishing conformity with the recently published MDR. The GSPRs are detailed in Annex I of the MDR. The GSPRs have replaced the Essential Requirements (ERs) found in Annex I of each of the former Medical Device

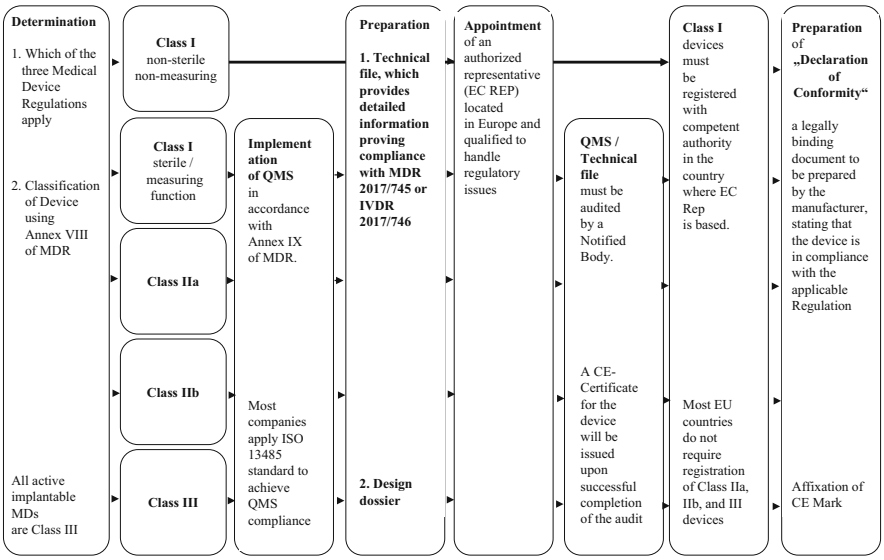

Fig. 13.3 Overall procedure for obtaining the CE Mark on a medical device. *QMS:* Quality Management System, *MDR:* Medical Devices Regulation, *IVDR:* in vitro Diagnostic Regulation

Directive (MDD) and former Active Implantable Medical Device Directive (AIMDD).

The basic philosophy is that the higher the risk of the device, the greater shall be the guarantees for safety for the device production provided by the manufacturer. The entire procedure for obtaining a CE Mark on a device is depicted in Fig. 13.3, starting from the initial step of device classification, up to the final step of affixing the CE Mark on the device itself.

For Class I equipment, the manufacturer could mark the product and put it into the market after writing a "CE declaration of conformity" to the General Safety and Performance Requirements. Through such a document, the manufacturer guarantees and declares that his products fulfill the Regulation requirements. However, the company shall have available all the technical documentation suitable to demonstrate the safety of the produced product. The "CE conformity declaration" is the simplest procedure of the CE mark. It deals with a simply declaration of assumption of responsability, without the intervention of a Notified Body.

13.3 Regulation (EU) No. 2017/745

As a mere example of application, the EU Regulation 2017/745 of the European Parliament and of the Council of 5 April 2017 concerning medical devices (hereinafter, the "MDR") repealing Directive 90/385/EEC (hereinafter, the "AIMDD") and

Directive 93/42/EEC (hereinafter, the "MDD"), is here reported. Such a regulation entered into force on 25 May 2017. As stated by EU Regulation no. 2020/561 of 23 April 2020, the MDR will come into force from 26 May 2021 on.

The MDR regulates:

- Medical devices for human use and their accessories (ref. art. 1, p.1 of the MDR);
- Device not placed on the market but used in the context of a commercial activity to provide a diagnostic or therapeutic service through information delivered and stored by services companies or other means of communication (ref. art. 6 of the MDR);
- Products that are not intended for medical use and listed in Annex XVI (ref. art. 1, p. 2 and Annex XVI of the MDR).

From May 27, 2024, only medical devices conforming to the MDR with a valid EU certificate of conformity issued in accordance with the MDR may be placed on the market.

13.3.1 Classification of Devices and Conformity Assessment Procedures

The Devices are divided into four risk classes I, IIA, IIB, III according to their intended use and the risks involved.

The classification is carried out by the Manufacturer according to the criteria of Annex VIII of the MDR (ref. art. 51 of the MDR).

Before placing a device on the market or in service, the manufacturer must assess the conformity of the device in accordance with the applicable conformity assessment procedures set out in Annexes IX to XI (ref. art. 52 of the MDR).

The conformity assessment procedures applicable to each class of risk are set out Table 13.1.

If the conformity assessment procedure requires the intervention of a Notified Body, the Manufacturer (or its Authorised Representative) submits an Application for Certification to a designated Notified Body of its choice (see Table 13.2).

13.4 Key Aspects of the New Medical Device Regulation (MDR)

- It introduces new classification rules and modifies some of the former MDD rules, making the classification criteria more stringent (ref. Annex XVIII of the MDR).
- It has four risk classes: I, IIA, IIB and III (Active implantable medical devices are in Class III).

Table 13.1 Conformity assessment procedures applicable to each MD class of risk

Device class	Conformity assessment procedure (MDR Annexes)	Intervention of the notified body
I (non-sterile, without measuring function, nonreusable surgical instrument)	Declaration of conformity (Annex IV)	Not required
I sterile (IS) I with measurement function (IM) I Reusable surgical instrument (IR)	– Annex IX—chapter I *or* – Annex XI—part A	Yes, the intervention of the Notified Body is limited respectively to:-"aspects relating to establishing, securing and maintaining sterile conditions";—aspects relating to the conformity of the Device with the metrological requirements;—aspects relating to the reuse of the Device (cleaning, disinfection, sterilisation, maintenance and functional testing and the related instructions for use)
IIa	– Annex IX—chapter I *or* – Annex XI—Part A *or* – Annex XI—Part B	Yes
IIb (non-implantable)	– Annexo IX—chapter I *or* – Annex X combined with Annex XI—Part A *or* – Annex X combined with Annex XI—Part B	Yes
IIb implantable[a] III	– Annex IX chapter II combined with Annex IX—chapter I *or* – Annex X combined with Annex XI—Part A *or* – Annex X combined with Annex XI—Part B	Yes

[a]Annex IX—Chapter II does not apply to the following implantable Devices: sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors

- It introduces economic operators (Manufacturer, Authorised Representative, Importer and Distributor) and defines their specific obligations.
- It introduces the need for the Manufacturer to have financial coverage and a person responsible for compliance.
- It strengthens the need for the Manufacturer to have: a risk management system; a post-market surveillance system; a system for reporting incidents.

Table 13.2 The conformity assessment procedures as set out in Annexes IX–XI. (*QMS:* Quality Management System)

MDR Annex		MDR conformity assessment procedure		MDR certificate	Corresponding MDD/AIMDD Annex
Annex IX	*Annex IX chapter II*	Device design assessment	Assessment of the Device technical documentation	EU technical documentation assessment certificate	Annex II.4
	Annex IX chapter I	Assessment of the quality system (complete)	Assessment of the complete quality system applied to all phases—design, manufacture and final control of the product, with verification of the technical documentation of the Devices covered by this QMS	EU quality management system certificate	Annex II except 4
Annex X		Product assessment	Assessment of the technical documentation of the Type and Performance of tests on a representative example of a given production (type verification)	EU type-examination certificate	Annex III
Annex XI—part A		Assessment of the quality system production quality assurance)	Assessment of the quality system applied to the manufacturing phase of the product, including verification of the technical documentation of the Devices covered by this QMS	EU quality assurance certificate	Annex V
Annex XI—part B		Product assessment (related to production)	Assessment of the technical documentation of the Device and Performance of tests on each individual product	EU product verification certificate	Annex IV (verification of each Device)

- It strengthens the need for the Manufacturer to demonstrate compliance with clinical data.
- It introduces the drafting of specific documents by the Manufacturer: Safety and clinical performance summary for Class III Devices and Implantable Devices, Post-market surveillance report for Class I Devices and Periodic safety update

report for Class IIA, IIB and III Devices; Trend reporting; Card for patients with implantable devices.
- It strengthens the concept of traceability of devices with the creation of the UDI system.
- It strengthens the use of EUDAMED (European Database on Medical Devices) for the collection of Device information in a single European database.
- It eliminates conformity assessment procedures based on product quality assurance (Annex VI of the MDD) and statistical product verification (Annex IV of the MDD with sampling).

13.4.1 Quality Management System (QMS)

The conformity of Medical Devices and in vitro Diagnostic Medical Devices according to the European Union Regulations or (previously) Directives must be assessed before sales are permitted. One of the major requirements to prove conformity is the implementation of the Quality Management System (QMS) according ISO 9001 (general rules) and/or ISO 13485 (MD's) (2016) and ISO 14971 (Risk Management in MD's) (2019). Even if the EU Regulations do not mandate certification to ISO 9001 and/or ISO 13485, the preferred method to prove compliance to such standards is to seek its official certification which is issued by certifying organizations (Registrars or Notified Bodies). A very careful assessment of the company's Quality Management System by the Notified Body, together with the review of the required Technical Documentation, is a major element which the Notified Body takes into account to issue the certificate of conformity to the company product(s).

13.5 Ethical Aspects and Ethical Committees

The Ethical Committee for clinical trials of medicinal products and of Medical Devices is an independent body which has the responsibility to guarantee the protection of rights, safety, and well-being of subjects in the trial and to provide public warranties of such a protection. The Committee can be established inside one or more public health structures (or comparable others, such as hospitals), in conformity to the applicable discipline. Further, the Ethical Committee is formed, in agreement with the regional standards, inside the in-charge regional administration.

Ethical Committees can also have a consultive function in relation to ethical issues connected with the scientific and welfare activities. The purpose is to guarantee the protection and foster human subjects values, if these functions have not already been attributed to other specific organisms. Further, Ethical Committees may propose initiatives of training the health operators, in relation to bioethics matters.

As a European reference, Directive 2001/20/CE may be mentioned which is relative to the application of Good Manufacturing Practices in the execution of drug clinical experimentation in clinical use. In Italy, the D.M. 12th May 2006 has established the minimal requirements for the establishment, the organisation and the functioning of Ethical Committees. Finally, Ethical Committees are responsible:

- to make the revision and to express an opinion on the protocol under study.
- to evaluate the proposed significant amendments and to convey an opinion.
- to verify the identity of experimenters, of structures, of materials and methods to be employed.
- to obtain and support the informed consent of the participants to the clinical study.
- to make periodical re-evaluations of approved studies.

13.5.1 Ethical, Scientific and Methodological Evaluation of Clinical Studies

Ethical, scientific and methodological evaluation of clinical studies has a reference which is expressed by the previously mentioned Directive 2001/20/CE, and by Helsinki declaration, Oviedo convention, GCP requirements and by the updated guidelines of EMA, regarding the evaluation of efficacy of clinical trials.

Ethical problems are becoming more and more important and pervasive in all human activities in healthcare. As far as scientific research is involved, there is also an "utilitarian" aspect to be considered: no scientific journal publishes now a research, an experimental or a developmental paper implying human subjects or animals without the approval of an Ethical Committee.

It is clear that the regulatory aspects of MD and IVD-MD are fully covered by proper EU Laws (Regulations) as well as by proper Technical Standards issued by qualified Committees of IEC and ISO. Most of these standards, related to the topic of MD and IVD-MD are also incorporated into European technical legislation as Mandate Standards. It has not been always managed in this way. Some decades have been required to reach such a rational organisation of EU Laws and acknowledged Technical Standards. It was necessary to make a long journey to reach this point, also passing from the "regime" of *EU Directives* to the one of *EU Regulations* on 2017.

Taking into account ethical aspects we may reasonably start from the ten points of the *Nuremberg Code.* This Code is constituted by a set of research ethical principles for human experimentation created as a result of the Nuremberg trials against members of German Nazi party, responsible for a variety of war crimes during the World War II. In particular, the so-called *Doctors' Trial* gave rise to the delivery of a Code (in 1947) which included innovative principles such as:

- Informed consent
- Absence of coercion
- Properly formulated scientific experimentation
- Beneficence towards passive participants involved in the experiment.

This concept is mainly based on the *Hippocratic Oath*, which was interpreted as endorsing the experimental approach to medicine while protecting the patient.

The ten points which constitute the Code are:

1. The **voluntary**, **well-informed**, **understanding consent** of the human subject in a **full legal capacity is required**.
2. The experiment should aim at **positive results** for the society that cannot be procured in some other way.
3. It should be based on **previous knowledge** (e.g. an expectation derived from animal and pre-clinical trials) that justifies the experiment.
4. The experiment should be set up in a way that **avoids unnecessary physical and mental suffering** and injuries to the passive participants (human or animal).
5. It should not be conducted when there is any reason to believe that it implies a **risk of death or disabling injury**.
6. The **risks** of the experiment should be in **proportion** to (that is, not exceed) the **expected humanitarian benefits**.
7. Preparations and facilities must be provided that adequately **protect the subjects against the experiment's risks**.
8. **The staff** who conduct or take part in the experiment must be **fully trained and scientifically qualified**.
9. The human subjects must be free to immediately **quit the experiment** at any point when they feel physically or mentally unable to go on.
10. Likewise, the medical staff must **stop the experiment** at any point when they observe that continuation would be dangerous.

13.5.2 European Regulation on Clinical Trials: Towards the Harmonisation of Standards on Clinical Trials

Regulation n. 536/2014 dated on 16th April 2014, on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC has entered into force in 2019.

The Regulation will ensure a greater level of harmonisation of the rules for conducting clinical trials throughout the EU. It introduces an authorisation procedure based on a single submission via a single EU portal, an assessment procedure leading to a single decision, rules on the protection of subjects and informed consent, and transparency requirements.

It will also make it easier for pharmaceutical companies to conduct multinational clinical trials, which should increase the number of studies conducted within the EU. The general principle is outlined in Art. 3 of the above-mentioned regulation.

A clinical trial may be conducted only if: (a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and (b) it is designed to generate reliable and robust data.

To improve data transparency from clinical trials, a European public and accessible databank of detailed abstracts (including final relations) will be available once a final decision is taken for the market submission or when an authorisation is rejected.

No application disclosure will be anymore accepted among European Member States. The strengthpoints are: (1) unique evaluation of a clinical trial, shared by all the Member States , (2) unique portal and European database directly managed by EMA and (3) unique access point for the documentation delivery and access.

Finally, it is worth to remember that also Regulation EU 2016/679, 27th April 2016, "General Data Protection-GDPR, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data", is mandatorily active from 25th May 2018. Particular attention is dedicated to *Health Data* (anagrafic, from medical record, biometric, genetic). A DPO (Data Protection Officer) is also foreseen who could be involved within 72 h from the possible violation to be notified to Privacy Authority. There is also mention to Accountability Commitments (at various levels) in the collection of these personal data.

For a complete implementation of DGPR, at least in Italy, we will have a National Law + Advice from Italian Privacy Authority.

It is worth to remember that an Ethical Committee must be interdisciplinary, i.e. is constituted by different experts from various areas. As an example, the Ethical Committee of the European Institute of Oncology and the Cardiological Institute in Milan is constituted by experts in the following areas or specialities:

Cardiosurgery, Pharmacology, Bioethics, Profession in Health, Biomedical Engineering, Genetics, Surgery, Biostatistics, Volunteering and patient safeguard, Clinical Oncology, Clinical Cardiology, Legal and insurance, Pharmaregulation, Pharmacy management, General Medicine, Pediatry.

Conclusion

The area of **Pharmaceutical Drugs** and **Medical Devices** is very complex, but has the characteristics of being *ruled* by *European Laws (Regulations)* and *Technical Standards*. Appropriate skills are required to correctly manage the various processes involved. The various and different skills of the involved stakeholders must be integrated with the adequate management actions.

On many occasions, it is the whole system that is inefficient and not very available to innovation. As an example, a major effort should be dedicated to improve its efficiency and efficacy through innovative measures relative to electronic informed consent, unified standards for the EHR, greater participation of the patient with perception of better control over her/his health situation and, finally, greater cooperation between trial researchers and treating physicians.

An important reference point, according to the official GCP document, is that two paper documents are still required. One for the patient and one for the clinical structure. Are we ready to move to fully computerised solutions? There are certainly

some regulatory, legal, insurance aspects and constraints, and others which still require documents in paper.

The developments of ICT-related techniques on the one hand and the considerable sociological change that will occur in the coming years (increase in the elderly population, increase in diseases linked to chronicity, different composition of the Italian/European population, lower activity in the hospital and greater activity on the territory and in the home environment, etc.) will be a challenge that must be won with a visionary, efficient and effective concept. It must involve all the actors on the scene of the Health System in order to create well-being for the entire population, not only **to increase the years of life**, but *improve life in living years* (QoL).

Regarding ethical Issues and the role of the Ethical Committees, it is fundamental to preliminarily think of the Patient to provide him with a "*Simple, Explicit, Free, Personal, Conscious and Manifest, Preventive, Specific and Confidential report*" and to represent *her/his interests* in front of very powerful stakeholders (companies, researchers, representatives of healthcare systems and political decision makers).

Among the major problems encountered into the field, it is important to remark the following aspects:

- Compromise to be reached between scientific development and benefit to the patient.
- Compromise to be reached between privacy and security problems and the advantage of data-sharing.
- Ethical and methodological aspects of Trials vs Placebo.
- Informed Consent [the e-consent is actually strongly encouraged]
- "Precision Medicine" vs "Protocol-Based Medicine" (!)
- Ethical dilemmas (efficient cost/benefit analysis before choosing a therapeutical procedure)
- To think preliminarily of the Patient; to find optimal tools of analysis: it was quoted that Google is better than WHO for the prediction of flu epidemies (!!??)
- Fundamental message: ethical problems must NOT be felt like a constraint, rather as a developmental motor to innovation (devices and instruments built according to a "people-oriented" paradigm.

The final objective is to be able to fulfill an "**Integral Ecology**", starting from "*Laudato si', sulla Cura della Casa Comune*" (*Praise Be to You - on Care for our Common Home*), expressed in the second Encyclical letter of Pope Francis, 2015 [8].

There, the concept of "Integral Ethics" is introduced: a triad Man, Animal, Nature has to be maintained for the well-being of All. Finally, there is a "Unique Tale" on the origin of Universe and hence of our planet. There is only one genealogic tree which gathers together all the living beings (including Man). The first Book that God wrote were not the Holy Texts, but the Cosmos.

Take Home Message

- Ethics is a very relevant issue when dealing with pharmaceutical drugs, medical devices, apparatuses and systems. Like drugs, the field of medical devices is strictly regulated by Laws (Regulations) and Technical Standards. Appropriate skills are required to correctly manage the various processes involved.
- When dealing with the development of medical devices, the right compromise must be reached between scientific and technological development and benefit to the patient. In addition, the conciliation between patient's privacy and security and the advantage of data-sharing should be considered.
- The evaluation of the cost/benefit ratio for the selection of a therapeutical procedure, including a risk analysis, should also be considered as an ethical aspect.
- Ethical considerations are not a constraint, but should be considered as a developmental motor for innovation. Medical devices and instruments must be built following a "people-oriented" paradigm.

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