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Quality Standards

This chapter discusses the following:

- What quality is
- Which mandatory and voluntary quality standards various industries use
- What these standards say about IT systems

1.1 What Quality Is

Quality is defined in the International Organization for Standardization (ISO) standard 8402 [1] as 'The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs.'

Quality is defined in the *Concise Oxford Dictionary* [2] as 'possessing high degree of excellence, concerned with maintenance of high quality (Quality Control).'

There will always be subjectivity involved when defining whether something has good, not so good, or bad quality. As ISO states, it also has something to do with 'implied needs,' which definitely will change over time. Forty years ago, a quality car had good seats, a working engine, and room for the luggage in the back; cars did not have air conditioning, seat belts, or airbags at that time. Today, any 'quality car' has all of these features as standard, and new inventions such as GPS may be considered a quality feature. In 10 years' time, this will probably be standard quality, while the new development will be electronics to prevent collisions.

So how do we define quality, apart from the definition of the word itself?

There are many standards around the world that govern quality and define what is needed in order to have a quality product. Some are mandatory to specific industries, while others

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are optional. Some are international; others are national; some are based around a political entity, such as the European Union (EU) or the Organization for Economic Cooperation and Development (OECD); and some are independent, such as the International Organization for Standardization.

Each company or organization will need to have a quality system to explain exactly how it wants to work in order to create and produce quality goods or services according to the standard that it needs to follow.

The lack of proper standards can result in large costs when batches or studies have to be reproduced or redone. Philip B. Crosby [3] has written: 'Quality is free. It is not a gift, but it is free. What costs money are the unquality things – all the actions that involve not doing jobs right the first time.' The way to avoid these costs is not to cause them in the first place, and that implies creating systems to explain in detail how to work in order not to make costly mistakes.

Quality assurance isn't something to learn in a week-long class and read about in ISO, GMP, GLP, GCP, or other quality standards. Unfortunately, it is also rarely taught in schools and universities, but today at least people recognize the expression.

It takes a long time to become a good Quality Assurance person. Knowledge of the standards is of course necessary, but even more so is the acquired feel for the 'quality way' of thinking, understanding, and seeing. The good QA people know the art of writing good Standard Operating Procedures (SOPs) and other quality documents, know ways of expressing themselves, and understand the consequences of the lack of quality. They are also able to see what is missing and what could be done better in any quality system. Quality assurance has grown to be a part of the person.

1.2 Mandatory and Voluntary Standards

Some industries are required to follow specific standards, while others may follow standards if they want to. Some examples are given below:

- The regulated industries include the pharmaceutical and nuclear sectors: Both are important in terms of public health and safety. Several of the standards that they follow are international. The controlling organs include the EU for products/production in the European market and the United States for products/production in the US market. The authorities require the industries to follow these standards, and can punish companies if they fail to do so. If a pharmaceutical company isn't in compliance with the standards, it can lose the license to sell its products; this, of course, is financially devastating to the company
- Semiregulated industries include healthcare, where there are large differences between the various countries. The controlling organs are national control bodies
- Nonregulated industries may want to follow a standard because it gives them a competitive edge. They may want to obtain a certification or accreditation to prove that they follow the standard. The controlling organs are accreditation and certification bodies

1.3 Pharmaceutical Industry Regulations

Three good practices cover the pharmaceutical industry:

- Good Manufacturing Practice (GMP), which covers manufacture and Quality Control of the products
- Good Laboratory Practice (GLP), which covers nonclinical testing of the products
- Good Clinical Practice (GCP), which covers clinical testing on humans

The acronym GxP is quite often used to cover one, two, or all three of GMP, GLP, and GCP.

It would be relatively easy to follow these standards if there were only the three GxPs, but there's more than one of each. The EU, the United States, Japan, Australia, and the OECD – just to mention a few – each have their own set of GxPs. Each company has to comply with the GxP in each market where it wants to sell its goods. So even if the company is manufacturing in Europe, it will need to comply with the US regulations when trading in the US market. Companies marketing world-wide must comply with all standards world-wide.

Many countries are trying to harmonize the standards. Europe has been able to get rid of the Nordic, German, British, and other GxPs and has replaced them with a European GxP. The United States, Japan, and the EU are working together in the International Conference on Harmonisation (ICH). The ICH is a cooperative effort between the drug regulatory authorities and the pharmaceutical organizations to reduce the need to duplicate the testing conducted during the research and development of new medicines, while at the same time maintaining the quality, safety, and effectiveness of those medicines.

Additionally, the authorities – not to mention the companies themselves – would like to see that once one agency has finished inspection, the others will accept this and not reinspect. The EU has established the European Medicines Agency (EMEA) (www.emea.eu.int). The EMEA has worked for a Mutual Recognition Agreement with Canada and Japan in its Work Program (December 2004), and the United States is currently working its way into this cooperative venture.

1.4 US GxP Regulations

All products on the US market must be made and tested according to the US regulations, regardless of the production site or country where the organization is legally registered.

Chapter 21 of the Code of Federal Regulations (21 CFR) describes the laws and regulations covering the pharmaceutical industry, which are numbered as 'Part xxx.' All regulation documents and guidance documents can be downloaded from the FDA homepage (www.fda.gov).

Due to the US Freedom of Information Act, the inspection results are also available to the public and can be found on the FDA home page. The 'warning letters' say a lot about what the inspectors are looking for and how they interpret the regulations at any given time.

Below is a list of regulations, but there are many more; these are outside the scope of this book. Some cover New Drug Approval (21 CFR Parts 312, 314, and 511), while others cover how to set up and conduct clinical trials, ensuring patient safety in clinical trials, and more.

1.5 European GxP Regulations

All products on the European market must be made and tested according to the European regulations, regardless of the production site or country where the organization is legally registered. The regulations cover all countries in the European Union as well as the European Economic Area (EEA) countries Norway, Iceland, and Liechtenstein. Switzerland is a large producer of pharmaceutical products, so even though it isn't a member of the EU or the EEA, the European regulations apply because Swiss products are exported to the EU.

The EU regulations can be downloaded from the Web (http://www.pharmalaw.org/eu_laws.htm).

1.6 Other GxP Regulations

Both Japan and Australia have started mutual recognition discussions with the EU through the EMEA and the ICH.

1.7 Good Manufacturing Practice

Good Manufacturing Practice (GMP) covers requirements for the manufacturing and quality testing of products. This includes everything from raw materials and production, through laboratory testing, to labeling and packaging.

1.7.1 US GMP

The latest GMP issued features one major change: the use of a risk-based approach so that the organization can analyze risks and determine where it needs to add effort and control. This has also made it possible to use Process Analysis Technology (PAT) to help the organization understand its processes. The risk management is based on the ICH Draft Consensus Guideline Q9 Quality Risk Management [4]:

21 CFR Part 210	*Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General* [5].
21 CFR Part 211	*Current Good Manufacturing Practice for Finished Pharmaceuticals* [6].

There are several more detailed parts to the GMP. The list below is not complete:

- Active Pharmaceutical Ingredients: ICH Q7A *Guidance to Industry GMP for Active Pharmaceutical Ingredients* [7]
- *Draft Guidance to Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* (draft, September 2004) [[8]
- Parts covering New Drug Approval, GMP for Blood and blood components, and others

- The FDA has also teamed up with the ASTM to create a *Standard Guide for Specification, Design and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* [9]

1.7.2 EU GMP

Volume 4 – *Good Manufacturing Practices – Medicinal Products for Human and Veterinary Use* [10].

1.8 Good Laboratory Practice

Good Laboratory Practice (GLP) covers the nonclinical testing of the products, but not the production-quality laboratory. Nonclinical testing includes the testing done on animals. Whether people agree with the practice or not, animal testing is required before the company can obtain a license to sell the product. The GLP has strict requirements for how the animals are to be treated and how data is to be secured and handled.

1.8.1 US GLP

21 CFR Part 58 Good Laboratory Practice for Nonclinical Laboratory Studies [11].

This document does not include the word 'computer' or any of its synonyms. However, there is a chapter on equipment. It is easy to see that computer systems are included in the expression 'equipment,' and that they need to be validated (appropriate design/function according to protocol/testing). Additionally, it is quite obvious that when a computerized system handles data for GLP, the requirements for the data will also apply to the system:

> *Equipment used in the generation, measurement, or assessment of data and equipment used for facility environmental control shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance. . . .*
>
> *Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.*

1.8.2 EU GLP

EU GLP *Council Directive of 7 June 1988 on the Inspection and Verification of Good Laboratory Practice (GLP)* (88/320/EEC) [12].

EU GLP *Council Directive – of 24 November 1986 – 86/609/EEC – on the approximation of laws, regulations, and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes* [13].

1.9 Good Clinical Practice

Good Clinical Practice (GCP) covers the clinical testing of the product: the testing on humans. The testing required before the company can obtain a license to sell the product is divided into three phases (I, II, and III), each of which expands the number of patients included in the previous phase. Some of the testing is also required for a period after the product has received its license, and this is called phase IV.

1.9.1 US GCP

Clinical trials are covered in a number of parts of 21 CFR. Here are the most important ones:

21 CFR Part 50 *Human Subject Protection (Informed Consent)* [14].
21 CFR Part 54 *Financial Disclosure by Clinical Investigators* [15].
21 CFR Part 56 *Institutional Review Boards* [16].
21 CFR Part 312 *Investigational New Drug Application* [17].

On the FDA web page, *21 CFR Part 11 Electronic Records; Electronic Signatures* [18] is also listed for GCP regulations. 21 CFR Part 11 is discussed below.

1.9.2 EU GCP

EU GCP *Directive 2001/20/EC relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use* [19].
EU GCP *Directive 2001/20/EC of April 4, 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials* [20].

1.10 Medical Device Standards

Medical devices are categorized by their impact on the body. The lowest class I is comprised of items used externally – such as band-aids – and the highest class III is comprised of items used internally, to keep a person alive – such as pacemakers. It has also been suggested that cigarettes should be defined as medical devices 'used for inhaling poisonous smoke,' in order to regulate the tobacco industry in the United States, but this hasn't happened yet. Whether or not this was meant to be a joke isn't known.

According to EU Council Directive 93/42/EEC of June 14, 1993 [21], a medical device is defined as follows:

> *(a) 'medical device' means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:*

- *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation 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;

(b) 'accessory' means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device;

(c) 'device used for in vitro diagnosis' means any device which is a reagent, reagent product, kit, instrument, equipment or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of samples derived from the human body with a view to providing information on the physiological state, state of health or disease, or congenital abnormality thereof;

The EU classification system for medical devices has three classes as defined in EU Council Directive 93/42/EEC of June 14, 1993:

Class I: Non-invasive devices

Class II: Surgically invasive devices intended for transient use

Active therapeutic devices intended to administer or exchange energy
Implantable devices and long-term surgically invasive devices
Devices used for contraception or the prevention of the transmission of sexually transmitted diseases

Class III: Invasive devices

Devices incorporating, as an integral part, a substance which, if used separately, can be considered to be a medicinal product, and which is liable to act on the human body with action ancillary to that of the devices.
Contraception or the prevention of the transmission of sexually transmitted diseases if they are implantable or long-term invasive devices.

Note that this is not a complete list; please see the directive for additional details.

The US classification system for medical devices has three classes, as defined in 21 CFR 860 [22]:

A device is in class I: . . . the device is not life-supporting or life-sustaining or for a use which is of substantial importance in preventing impairment of human health, and which does not present a potential unreasonable risk of illness of injury.

A device is in class II: . . . use in supporting or sustaining human life . . .

A device is in class III: . . . the device is life-supporting or life-sustaining, or for a use which is of substantial importance in preventing impairment of human health, or if the device presents a potential unreasonable risk of illness or injury.

1.10.1 The US Medical Device

There are several parts of 21 CFR that cover medical devices. The most important ones are listed below.

21 CFR Part 803 *Medical Device Reporting*.
21 CFR Part 806 *Medical Device Reports of Corrections and Removals*.
21 CFR Part 820 *Medical Devices Quality Systems Regulations* [23].
21 CFR Part 821 *Medical Device Tracking Requirements*.
21 CFR Part 860 *Medical Device Classification Procedure*.

For more information, check the FDA web page.

1.10.2 The EU Medical Device

The EU has two main Council directives covering medical devices:

Council Directive 93/42/EEC of June 14, 1993, concerning medical devices.
Council Directive 90/385/EEC of June 20, 1990, on the approximation of the laws of the Member States relating to active implantable medical devices [24].

1.11 IT Systems in the GxP and Medical Device Regulations

IT systems may have a direct or indirect impact on product quality in various ways. Such IT systems are generally called GxP systems. Systems may have an indirect impact if they handle the quality system and the Standard Operating Procedures, or a more direct impact if they handle production and validation documents. GxP systems with a direct impact include, but are not limited to, the handling of raw materials used in the production, production planning, and control systems; laboratory systems; and clinical systems.

The GxPs themselves don't say very much about IT systems, so the authorities have created amendments and/or added standards to make companies understand how they are expected to handle IT systems. In an old version of the EU GCP in the early 1990s, the only requirement for computer systems was that 'Computer systems shall be validated and error free.' The next version had removed the requirement 'error free . . .'. The current version doesn't even mention computers.

IT systems for medical devices are used in two entirely different ways. The first is when the IT system is used for the development, production, and control of the medical device – just as it is for any pharmaceutical company. It must then be handled in the same way as IT systems are handled in GxP. The second is when the IT system is the medical device itself. Some medical devices – for example, pacemakers – are implanted in the body. Others are used for *in vitro* (outside of the body) testing – for example, testing for allergies – where the test instrument is regarded as a medical device.

An IT system is often regarded as a quality challenge. In the industry, people have their degrees and training in biology, chemistry, and pharmacy, with specialization in production processes, analytical laboratory work, and so on. An IT system is regarded as a tool to

help the scientists do the work that they understand. While the scientists understand what the system does, they don't know how it has been programmed or how it works, and they find it difficult to handle from the point of view of Quality Assurance. The object of this book is to make non-IT people able to handle IT systems even without programming knowledge.

1.11.1 US IT Regulations

Guidance for Industry on Computerized Systems Used in Clinical Trials [25]:

21 CFR Part 11 *Electronic Records; Electronic Signatures*.

In the 1990s the pharmaceutical industry wanted a guideline for electronic signatures. The FDA created the *21 CFR Part 11 Electronic Records; Electronic Signatures*. The first draft was made public and received a lot of comments, some of which were contradictory, but all were included in the preamble of the final rule when it was published on March 20, 1997. The FDA expected that the industry should be able to comply with the rule within four months – by August 20, 1997. The industry was surprised to see that very little of the regulation actually covered the electronic signatures, while the majority of the text covered electronic records. However, that does make sense: You can only trust the electronic signature if the electronic records can be trusted. For more details on 21 CFR Part 11, please refer to Chapter 2.

1.11.2 EU IT Regulations

Details of the EU regulations for IT systems can be found in Chapter 2. What follows is only a short overview.

GMP: The EU GMP added Annex 11 to explain what the regulators thought was needed for computerized systems. Annex 11 has 19 clauses covering what the inspectors expect from the industry, but it isn't very useful as a tool to understand how thee requirements can be accomplished. Annex 11 originated as PIC GMP Annex 5 in 1991 and was later adopted by the EU GMP as Annex 11. As of January 2008, the GMP Annex 11 is still the current requirement for IT systems – considering the speed at which technology has improved since this document was created, it is about time for Annex 11 to be revised.

The Pharmaceutical Inspection Cooperation Scheme (PIC/S; see www.picscheme.org) is the organization for inspectors from a total of 31 countries, including most of the European countries, Australia, and Canada, but not the United States. The inspectors also thought that it was about time to revise Annex 11, especially after the FDA had created the 21 CFR Part 11, with its detailed requirements.

The PIC/S finalized their document under the name *PI 011-01 Good Practices for Computerized Systems in Regulated 'GxP' Environments*. The current version is now PI 011-03 [26]. There is a precedent for PIC/S documents to be included in the EU GxP, as we have seen with PIC/S GMP Annex 5, which became EU GMP Annex 11, so we can expect this document to become an annex to the GxPs in the future. When the inspectors get together and create a document like this, it is worth paying attention to it.

GLP has long used the OECD Monograph 116 [27] for the pharmaceutical industry, which contains more detail than the old GMP Annex 11. The new PIC/S document also covers GLP.

GCP has adopted the GMP Annex 11, but the new PIC/S document also covers GCP.

1.12 GAMP

Good Automated Manufacturing Practice (GAMP) was started as a private initiative to explain to the pharmaceutical industry what was needed of IT systems validation in order to fulfill the regulatory requirements, since these requirements were very hard to translate into 'what do we actually do to validate our computer system.' More than 10 years later, GAMP is now an industry standard, endorsed by the FDA. This has transformed GAMP from a guideline to a more or less mandatory standard. The current version is *GAMP 5 Good Automated Manufacturing Practice* [28].

The GAMP organization is a voluntary body, in which many people around the world take part in preparing various standards and good practices under the International Society for Pharmaceutical Engineering (ISPE) umbrella. The result is that GAMP has issued several guidelines as answers to the new regulatory initiatives:

- the Part 11 risk-based approach to validation [29]
- the laboratory instruments guide [30]
- the testing of GxP critical systems [31]
- global information systems [32]
- calibration management [33]
- the infrastructure guide [34]
- process control systems [35]
- the archiving of electronic data [36]

GAMP is currently working on several new guides. There are also smaller guides called Position Papers, which include a guide for Building Management Systems [37].

Standards usually cater to one specific type of organization. For example, the ISO 9000 series is meant for manufacturers; the GxP standards are meant for pharmaceutical development, testing, and production; and the PIC/S standards are meant for pharmaceutical inspectors. GAMP is the only standard that caters to them all. It has chapters for the developers of the system – that is, the suppliers – on how to develop the system in a GxP environment; chapters for the QA inspectors, so that they will know what to look for when doing a supplier audit; and chapters for the end-users, so they will know what to do with, for example, validation of their system.

1.13 Mandatory Quality Standards in Other Industries

The *nuclear industry* is often thought of as the nuclear power industry, but also other industries can also fall into this category. There are nuclear research facilities, and nuclear pharmaceuticals for use in diagnostics and cancer treatment. The production facilities of these industries are also covered in the nuclear regulations, in addition to the GMP.

Transport of nuclear material is also a potential health hazard, which is covered by health, environmental, and other safety regulations.

In the United States, the nuclear industry is covered in 10 CFR, and governed by the US Nuclear Regulatory Commission (www.nrc.gov).

Healthcare is a national activity and is governed by national laws.

In the United States, most healthcare facilities – such as hospitals – are private. The governmental US Occupational Safety and Health Administration (OSHA; see www.osha.gov) has requirements for how these are to be handled.

In many European countries, the hospital system is governmental, and quality requirements are rarely as strict when it is the government that has to pay for compliance, rather than private organizations. The laws governing healthcare are mainly national laws.

In most countries, there are also regulations for how patient data is to be treated to maintain confidentiality.

1.13.1 The Food Industry

The US FDA covers both food and medicines in its GxP standards. The FDA also has its own Center for Food Safety and Applied Nutrition (CFSAN). Their web page (www.cfsan.fda.gov) includes all regulations for foods and cosmetics.

In Europe, the EU has created an integrated approach to food safety that aims to assure a high level of food safety, animal health, animal welfare, and plant health within the European Union. The food regulations are managed by the European Food and Safety Authority (EFSA). More information can be found on their web page (http://www.ec.europa.eu/food/index_en.htm).

1.13.2 GALP – The Environmental Standard in the United States

The US Environmental Protection Agency (EPA) has issued standards for Good Automation Laboratory Practices – GALP [38]. GALP is mandatory for all industries in the United States, but is only relevant for industries that are actually producing in the United States. More information can be found in a book on GALP written by Dr Sandy Weinberg [39].

1.13.3 Health, Environment, and Safety

The employees' health, safety, and work environment are also mandatory issues in many countries. These are legal obligations, which are usually governed by national laws rather than international laws. The IT systems taking care of these issues also need to be subject to control.

National standards and laws cover requirements for the health, environment, and safety of employees. These include requirements on health issues, such as a smoke-free work environment, the internal environment temperature, humidity, light and access to daylight; protection from chemicals and other harmful substances; and protection from physical hazards such as falling building materials in the construction industry or wet floors in a production environment.

The EU initiative for a directive for Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [40] (http://www.ec.europa.eu/enterprise/reach/index_en.htm) covers chemicals and their transportation, labeling, and use, to mention a few. When it is implemented, the directive will hopefully have a positive impact on chemicals on health, the environment, and safety.

1.14 Legal Issues

1.14.1 Finance

Regardless of the type of industry, there will normally be legal issues that have to be dealt with correctly. One is finance, where tax authorities have their say. IT systems taking care of book-keeping and financial transactions are also subject to scrutiny by the authorities – even if they don't form part of a GxP system.

Financial issues may be national or international, and include financial planning and reporting, economy and book-keeping, and taxation issues. IT systems are generally used for these purposes, and they need to be handled so that they yield correct results. However, there are no legal requirements to prove that the systems are correct.

1.14.2 Patents

Patents are important in the pharmaceutical, biotechnology, and medical device industries, as well as in other industries. While projects in early phases are not a part of the GxPs, it is important for companies to have their systems dealing with patent issues under control, to provide proof of discovery for patents. Electronic Lab Notebooks (ELN) are increasingly used in the work done prior to the patent application. When used correctly, these will provide better security for data than a paper laboratory notebook, as it is more difficult to be fraudulent. The ELN is described in Chapter 18.

1.15 The ISO

The International Organization for Standardization (ISO; see www.iso.org) is an international body that creates standards for the industry to use on a voluntary basis. It is possible to use some of the standards for accreditation and certification purposes, while others are guidelines or describe other issues.

Several national standards use translated ISO standards as their local standards. The ISO also implements good national standards as ISO standards. One example of that is the British Standard BS 7799 on IT security, which has been adopted as international standard ISO 17799 [41].

An organization can obtain a *certification* to show that it follows a quality standard. In many cases, this is an ISO 9001 certification, which proves that the organization has a quality system as described in ISO 9001 and that it is following it. The certification is issued by a 'certification body,' which has been accredited to do so by a national 'accreditation body,' such as the UK Accreditation Service (UKAS), Swedish Accreditation (Swedac),

and Norwegian Accreditation (Norsk Akkreditering), to mention a few. Most countries have one accreditation body and several certification bodies.

The ISO standards are named using the format ISO [standard number]:[approval year]. The newest version must always be used, but the certifications/accreditations may relate to an older version. However, the company must update to the newest version before the next certification/accreditation inspection.

The most commonly used ISO standards are the following:

- ISO 9000 [42]
- ISO 9001 [43] for certification
- ISO 9004 [44]
- ISO 14001 [45]

ISO 9000 describes requirements for a quality management system in a quality-managed organization.

ISO 9001 describes how to develop, manufacture, and test products, and covers relations between customers and suppliers. ISO 9001 is a certifiable standard. This means that a company that chooses to comply with the standard can get a certification body to assess its compliance and issue a certificate to prove that it is following the standard. ISO 9001 is useful for developing and manufacturing tangible things, but more difficult to use for intangible items such as software programs. ISO 90003 [46] is a guideline to ISO 9001 that explains how software can be developed according to ISO 9001. When IT suppliers want a certification for their system development, they will apply for an 'ISO 9001 under the TickIT scheme.' This basically uses ISO 90003 as a standard for the development of the system.

ISO 9004 offers guidance for the continuous improvement of a quality system.

ISO 14001 'specifies requirements for an environmental management system to enable an organization to develop and implement a policy and objectives which take into account legal requirements and other requirements to which the organization subscribes, and information about significant environmental aspects,' to quote the scope of the standard. It is closely linked to ISO 9001, to make it possible to create one quality system that covers both the environmental aspects and the quality-business aspects.

ISO 14971:2007 covers risk assessment for medical devices [47].

Accreditation is more than a certification, as the standards for accreditation also require competence in the process. One of the accreditation standards is the Laboratory accreditation standard ISO 17025 [48].

1.16 The ASTM

The American Society for Testing Materials (ASTM; see www.astm.org) is a standards organization that was started more than 100 years ago. Members volunteer to take part in creating, assessing, and maintaining standards within their field of expertise. Each standard is approved by member consensus and therefore reflects the current thinking in the industry.

The ASTM has several standards for laboratories and healthcare providers and producers, as well as for numerous other industries, including safety of toys and carousels, and quality and standards for steel alloys.

The most interesting standards in this context are those of Section 14 – General Methods and Instrumentation, which cover Healthcare Informatics, Computerized Systems, Chemical and Material Information, Forensic Sciences, Chromatography, and Laboratory Apparatus, just to mention a few.

The Laboratory Information Management System (LIMS) standard E 1578 [49] covers, among other things, terminology, the concept model, functions and workflow, database technology and structures, hardware platforms, and the life cycle. While this standard contains a lot of valuable information, there are also chapters that are rather outdated, given the nearly 15 years since it was first created. The functions defined as advanced in the document are standard features in almost every LIMS today.

1.17 The IEEE

The Institute for Electrical and Electronics Engineers (IEEE; see www.ieee.org) is another standards organization. The IEEE has many very good standards for software development and testing, among which are standards for:

- software verification and Validation Plans [50]
- software design descriptions [51]
- software reviews [52]

1.18 Tasks

1.18.1 Retrieve Standards

Retrieve the following standards from the US FDA web page (www.fda.gov):

- 21 CFR Part 210
- 21 CFR Part 211
- 21 CFR Part 820
- 21 CFR Part 58
- 21 CFR Part 11 with guidance document
- GCP

Retrieve the following standards from www.pharmacos.eudra.org:

- EU GMP
- EU GLP
- EU GCP
- EU GMP Annex 11

Retrieve the following standards from www.picscheme.org:

- PI-011-03 (or current version)

1.18.2 What do the Standards Say about IT Systems?

- Read through the various US GxP standards and see what these say about IT systems. Don't include 21 CFR Part 11 in this research
- Read through the various EU GxP standards and see what these say about IT systems. Don't include GMP Annex 11 or PI-011-03 in this research

1.18.3 A Comparison between the EU GMP and the US GMP 211

Compare the EU GMP and the US GMP and note similarities and differences.

1.18.4 What Must be Included in the QMS?

A QMS should cover all parts of the organization that will have an impact on the product quality. Discuss whether the following items have an impact on product quality and therefore should be included in the QMS:

- the process of employing new personnel
- the training and training records for the personnel
- equipment calibration
- equipment use
- internal environmental issues – for example, temperature and humidity in the offices
- internal environmental issues – for example, air pressure, temperature and humidity in sterile facilities
- safety issues – for example, how to handle chemicals
- personnel issues – for example, assessment of employees or salaries
- purchasing and invoicing

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