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Preface

The use of analytical sciences in the discovery, development and manufacture of pharmaceuticals is wide ranging. From the analysis of minute amounts of complex biological materials to the quality control of the final dosage form, the use of analytical technology covers an immense range of techniques and disciplines. This book concentrates on the analytical aspects of drug development and manufacture, focusing on the analysis of the active ingredient or drug substance. The book does not describe in detail the analysis of drug products – typically drug substances and excipients in a formulation. However, many of the approaches described for characterising drug substances can be applied to formulations, either by accounting for the presence of excipients in the analyte or by extracting and analysing the active ingredient.

The pharmaceutical industry is one of the most active areas for the application and development of new methods in the analytical sciences. This volume provides those joining the industry or other areas of pharmaceutical research with a source of reference to a broad range of techniques and their applications, allowing them to choose the most appropriate analytical technique for a particular purpose.

No book on the analysis of pharmaceutical materials should ignore the important area of quality and regulation. The first chapter provides an up-to-date overview of the philosophy and practicalities of working in a regulated environment, with reference to current regulations and guidance.

Subsequent chapters cover the major disciplines of separation sciences and spectroscopy. Recognising the importance and breadth of the area of separation sciences, our authors concentrate on method development in high performance liquid chromatography (HPLC or LC), capillary electrophoresis (CE), gas chromatography (GC) and thin layer chromatography (TLC), discussing traditional approaches in addition to the newer computational and chemometric methods.

One of the most important and challenging areas in the analysis of pharmaceuticals is the determination of chiral purity. It is therefore highly appropriate that a chapter is devoted to this area. The importance of chiral analysis is described, together with the development of techniques across the separation sciences and beyond.

In considering the spectroscopies, the development and widespread use of coupled techniques forms a major part of the volume in the chapters covering nuclear magnetic resonance (NMR) and mass spectrometry (MS). In the NMR

chapter, extensive coverage is given to state-of-the-art coupled LC/NMR. The chapter also covers multi-nuclear NMR, computer-aided spectral interpretation, quantitative NMR and solid-state NMR – all important techniques applied in the pharmaceutical development laboratory.

Recent years have seen many important developments in MS. This book devotes a chapter to the technique, focusing on the varied instrumental capabilities, their basic principles of operation and their applicability to pharmaceutical analysis. The applications of mass spectrometry, both in structure elucidation and quantitative analysis, are considered. Quantitative analysis MS is covered in detail, to allow the reader to gain background knowledge of a technique that is becoming important in drug substance analysis.

Vibrational spectrosopy can be used to support structural elucidation by NMR and MS, but more typically it is used for identity testing, because IR and Raman spectra act as a fingerprint for molecular structure. However, both IR and Raman find their principal application in the investigation of polymorphism. Examples are described in this chapter, together with the benefits of coupling these techniques to microscopy.

Additional solid-state techniques are covered in the chapter on solid-state analysis and polymorphism. The determination and control of the solid-state form, in respect of both crystal structure and particle characteristics, are important. The physical properties of the drug substance will influence its behaviour during handling processes and formulation, and can have a dramatic effect on dissolution, solubility and therefore bioavailability.

Although microscopy and imaging are used in a number of the above disciplines, a separate chapter is devoted to the use of optical and electron imaging techniques and image analysis, which play an increasingly important role in contaminant analysis and drug-excipient distribution.

The final chapter deals with the increasingly important area of process analytical science. There is increasing interest in in-process measurements from the FDA and other regulatory bodies, and this seems certain to be a rapidly expanding area of the analytical sciences in the pharmaceutical industry.

The regulatory, environmental, technological and commercial drivers in the pharmaceutical industry have profound implications for the analytical chemist. We hope that this volume, contributed by specialists from both the industrial and the academic sectors, will prove to be a useful source of reference for all those interested in this rapidly changing field of science.

David C. Lee
Michael L. Webb

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1 Quality control and regulation

C.J. Moores

1.1 Introduction

Any person working within the pharmaceutical industry or allied/support industries in a scientific capacity will be well aware that a good deal of their everyday work requires conformance to quality standards dictated by various regulatory bodies. For a scientist coming directly from university into the industry, there may well be some culture shock and bewilderment caused by the plethora of standards and procedures that require to be followed as part of their job. Additionally, it may be disturbing to discover that non-compliance with these quality standards and regulatory requirements could result in severe penalties for their employer and loss of their own job.

One of the major disciplines impacted by these requirements is the analytical sciences. The issue could arise in a variety of departments that either directly or indirectly provide data for the assessment of pharmaceutical materials or the support of various regulatory filings. These pharmaceutical materials could be drug products (the formulated dosage form), active pharmaceutical ingredients (API, also referred to as drug substance or bulk pharmaceutical chemical), raw materials, starting materials and intermediates used for the production of these pharmaceutical materials, or even materials derived from toxicology experiments. The filings could, for example, be for an investigational new drug application (IND), a new drug application (NDA) or a marketing authorisation application (MAA). This list is by no means exhaustive, but is meant to illustrate the variety of roles governed by regulatory bodies that may be encountered by an analyst within the pharmaceutical industry, whether in an R&D or a commercial environment. These terms will be explained more fully later when it will also become clear that every aspect of the work that analysts perform is influenced by the requirements of these regulatory bodies and the need for analysts to be able to defend their work.

This chapter provides an overview of the quality systems and regulations an analyst may encounter in the pharmaceutical industry and the reasons for these systems, as well as a description of the various regulatory bodies that they may have to interact with. The overview may serve as refresher training for those working in the industry at present, and as a tool to aid the understanding of the extent of regulation for those scientists thinking of entering the industry or who work outside of the pharmaceutical industry or in allied industries. The

most current detail of requirements may be found in the various references quoted, which will normally direct the reader to an appropriate website.

We shall concentrate on the area of new chemical entities (NCEs) rather that new biological entities or biopharmaceuticals. These latter materials are governed by very similar regulations and quality requirements, but are somewhat outside of the experience of the author. The focus will be on regulatory requirements in the USA and Europe.

1.2 The quality of medicines

1.2.1 The meaning of quality

I could not continue to discuss quality systems, regulation and regulatory bodies that have jurisdiction over the pharmaceutical industry, without first discussing the meaning of quality in the context of medicines and why quality and hence regulation, are so important both in the commercial and R&D environments.

Most people have their own subjective view of the meaning of *quality* in everyday life. When asked to define exactly what they understand by the term, then their definitions tend to be rather woolly and it is obvious that there are different meanings depending on the environment that the term is used in. The traditional view of *quality* derives from the inspection/measurement approach used in quality control when *quality* consists of conformity with a pre-determined specification. For example, 'quality is the degree to which a specific product conforms to a design or specification' [1]. The view of *quality*, especially within the context of the pharmaceutical industry and quality assurance, has now moved away from this rather narrow view, and the definition more or less accepted at present tends to be *fitness for purpose* [2]. The International Organisation for Standardisation (ISO) has further refined this definition in the application of the ISO 9000 quality standards to mean *fitness for purpose with customer satisfaction*. This is to take into account the fact that the ISO 9000 standard covers an extremely wide range of products and services where customer satisfaction is the main determinant of quality.

When this definition of *fitness for purpose* is applied to the pharmaceutical industry, it can be seen to fit well with the concepts of quality. Personnel have to be shown to be *fit for purpose* for the job they are employed to do (training, education and experience). Equipment needs to be demonstrated as *fit for purpose* based on qualification/validation, maintenance and calibration. Manufacturing processes are deemed *fit for purpose* based on in-process testing, process validation, etc. Process materials are shown to be *fit for purpose* based on testing appropriate to their intended use in the process. This use will vary depending on the stage of processing and whether it is a primary (chemical) process or a secondary (formulation) process.

1.2.2 Medicines are special

Why are medicines different from other consumer products? Why is there so much regulation of the pharmaceutical industry? Why, in the light of modern analytical techniques, can't we rely on thorough testing of the final product (end-product testing) and do away with all of these bureaucratic systems? These are just some of the questions that are always asked of quality professionals in the pharmaceutical industry and I will try and answer them.

Medicines are special because virtually no other product is consumed by the public on such utter trust – trust that the medicine will not do them more harm than the illness it is meant to cure. Their doctor prescribes the medicine; it is dispensed by a pharmacist and is taken by the patient in the belief that it will cure their ill health and that it will not make it worse! This trust can only be assured if the medicine has been adequately tested during development. This testing should assure that side effects have been established and that the medicine is efficacious. When the medicine is given to patients it must have been appropriately manufactured, tested and packaged to assure that:

- It is the correct product.
- It is the correct strength.
- It has not degraded.
- It is free from harmful impurities and micro-organisms.
- It has not been contaminated.
- It is correctly labelled.
- It is properly sealed in a suitable container.

1.2.3 End-product testing

End-product testing (quality control) is the reliance only on appropriate analytical tests to demonstrate the quality of a medicinal material. End-product testing alone is considered as *testing quality into the product*. You only accept those materials that pass specification. This is not adequate to ensure that the medicine is free from all manufacturing faults, that test methods employed are adequate to establish its purity and that a small proportion of defective materials would be detected. I will give several examples to illustrate this point.

Example 1.1. All pharmaceutical industry regulators prohibit the manufacture of penicillins in the same facility as other medicinal materials. The reason for this is the very high potential of extremely low levels of penicillin to cause serious side effects in individuals who are sensitised to this class of compounds. For this reason, cross-contamination levels are set at zero and the only way to ensure compliance is to not have the penicillin there in the first place. Firstly, the penicillin may contaminate at such a low level that existing analytical methods would not detect the presence of it, even if it were suspected of being

present. Secondly, the penicillin contamination may not be distributed evenly in the medicinal material, making detection very difficult.

Example 1.2. (This example is taken from a real incident.) A solution of a chemical intermediate used for the production of an API was stored temporarily whilst waiting further processing. The storage containers used had previously contained a potent pesticide that had not been completely removed. These pesticide residues continued through the whole process to the final drug product, without detection. Apparently, the chromophore of the pesticide was very different from that of the material under test at each stage of manufacture and the analytical methods being used could not detect these low levels of contamination.

In conclusion, end-product testing is not adequate for the following reasons:

- You only test for what you expect to find.
- You only test a small portion of the bulk of the test material. (There could be a small proportion of defective material in a batch, which only 100% testing would detect, e.g. microbiological contamination of sterile vials.)
- It is doubtful whether, in the case of medicines, the consumer would detect defects.

To assure the quality of medicinal products, quality must be built in at each stage of the manufacturing process and not merely tested in. Any factor that could have an effect on the quality of the final medicinal product must be controlled. These factors could be anything from the design of the production facility used or the environment the material is isolated in, to the analytical test methods employed at each stage of production. The philosophy of quality assurance is that batch to batch consistency should be maintained by reducing variability of all supporting processes, sub-processes and procedures. Hence, if written procedures control all of these factors and trained personnel follow these procedures, then a product consistently meeting its predetermined specification should be produced. End-product testing then becomes just a final check of the quality of the product. This testing is then used in conjunction with the written records, which demonstrate that all critical factors have been controlled, as the supporting documentation to allow the material to be released for use. This is what is meant by a quality system.

1.3 General quality system requirements

There are a number of quality systems that may be encountered by the pharmaceutical analyst but by and large the major one will be good manufacturing practice (GMP). Compliance to GMP is a requirement for the manufacture and testing of a drug product or API destined for human use, whether in the context

of commercial manufacture or a clinical trial. Similarly, data supporting non-clinical safety assessment of chemicals requires to be generated to good laboratory practice (GLP). The majority of other quality systems are voluntary and are commercially driven.

Before discussing the various quality systems encountered by the pharmaceutical analyst, I would like to more clearly define some of the quality terms that are used to ensure some consistency, as these definitions may vary depending on the quality system. These definitions are taken from the GMP guide for API, ICH Q7A [3] as there is a good chance that more than one interested group has input into the definition.

Quality control (QC): Checking or testing that specifications are met.

Quality assurance (QA): The sum total of the organised arrangements made with the objective of ensuring that all materials are of the quality required for their intended use and that quality systems are maintained.

Quality unit: An organisational unit, independent of production, which fulfils both QA and QC responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending on the size and structure of the organisation.

Quality: Fitness for purpose.

Good manufacturing practice (GMP): GMP is that part of QA which ensures products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation or product specification. GMP is concerned with both production and QA [4].

In previous sections, I have given a number of reasons why the whole aspect of medicine development, manufacture and testing requires to be performed in a different manner to that of any other product. There are many documented examples in the history of the pharmaceutical industry that demonstrate the necessity for regulations and regulatory bodies to oversee compliance to these regulations. There are cases of people being harmed by inadequate toxicity testing during development (e.g. thalidomide). There have been examples of the inadequacy of systems to ensure the integrity of tests performed in support of drug registration (resulting in the introduction of GLP). There have been not a few examples of the lack of assessment of the effect on the quality of drugs resulting from changes to the manufacturing environment and manufacturing route (resulting in the establishment of Good Manufacturing Practices Regulations). The establishment of these regulations has been independently mirrored outside of the pharmaceutical industry by the introduction of quality systems, such as ISO 9000, in an attempt to bring consistency of quality to other industries and services.

There is a common theme to all quality systems whether used for pharmaceutical production or not.

- The quality system must be described in written documents approved by management (policies, quality manual, etc).
- The quality system must be regularly reviewed.
- There must be senior management involvement in quality.
- All operations that can effect quality must be described in written and approved procedures (standard operating procedures, SOPs).
- Materials must be appropriately approved prior to use.
- Output (product) must be appropriately inspected prior to release.
- Equipment used must be fit for purpose (qualified/validated, calibrated and maintained).
- Personnel must be trained in the quality system and in operations they perform.
- Written records must be kept to demonstrate quality procedures have been followed.
- There must be regular internal quality audits to ensure quality is maintained.

In conclusion, all quality systems are to do with people, materials, equipment, records and procedures.

I will now give an overview of the quality systems that the analyst may come across while working in the pharmaceutical or allied industry, in either an R&D or a commercial environment.

1.3.1 ISO 9000

This quality standard is a voluntary standard operated by many industries worldwide. Compliance to this standard demonstrates to customers that defined systems have been followed for the design, manufacture and/or testing of products.

The ISO 9000 quality standard was developed from the original BS 5750 quality standards and was issued in 1987. The standard was adopted as a European standard, EN29000, in 1988, and is one set of a whole set of ISO standards. The main part of the ISO 9000 standard is made up of three separate standards:

ISO 9001 Covers design, development, production, installation and servicing.

This is the most comprehensive of the three ISO 9000 systems and is applicable to a supplier involved in original design. It is also commonly applicable to service activities where the service is being designed to meet specific requirement. This is typically found in contractors to the pharmaceutical industry where the development of a manufacturing process is performed. Similarly, it will be relevant to developers of computer software, although the ISO 9001-TickIT standard (specific to the development of software) would be more appropriate in this case.

ISO 9002 Covers production, installation and servicing.

This system is identical to ISO 9001 except it does not include the design part. This is the most common system used worldwide and can be applied to either manufacturing or service industries providing a standard product or service. A number of pharmaceutical manufacturers are certified to this standard.

ISO 9003 Covers final inspection and test.

This system has limited value and application as it encourages quality to be inspected in rather than designed in. It would be rare to find this standard applied within the pharmaceutical industry as the output of data is normally considered to be the provision of a service under ISO 9002.

These standards are operated as follows:
A national Accreditation Body, such as the United Kingdom Accreditation Service (UKAS), accredits a certification body (e.g. Lloyds, BSI, etc.) who in turn certifies individual companies that make a voluntary application to them. This certification is based on successful audits by trained ISO 9000 auditors. The company maintains its ISO standards by means of internal auditors and by annual or biannual audits and regular follow-up audits from the certification body.

These standards are a voluntary set of worldwide standards that a whole range of industries and services have adopted. Their relevance to the pharmaceutical industry has been questioned in the past, particularly by the USA Food and Drug Administration (FDA), on the basis that the system ensures consistency of development, manufacture and testing, but does not address the key issue of product quality, this being left to the customer and supplier to agree. However, these standards have been adopted by a number of pharmaceutical companies as a means of laying a quality foundation with respect to quality management and on which to base and support further quality systems such as GMP. The ISO 9000 quality systems will also be followed by the majority of material suppliers and contractors to the pharmaceutical industry where the use of these materials and services does not require compliance to a higher standard such as GLP or GMP. In fact, it would be unusual for most pharmaceutical industries to accept any of these materials or services from a company that did not follow the appropriate ISO 9000 standard. For these reasons it is important for those working in the pharmaceutical industry to have some understanding of these standards.

The latest up date of the ISO 9001 standard is ISO 9001–2000 and may be obtained via the ISO's Website [5].

1.3.2 UKAS

Analytical scientists may encounter UKAS in a number of work environments. UKAS is the sole national accreditation body recognised by government to assess, against internationally agreed standards, organisations that provide certification, testing, inspection and calibration services. UKAS is a non-profit-distributing

company, limited by guarantee, and operates under a memorandum of understanding with the government through the Secretary of State for Trade and Industry [6].

The knowledge that conformity assessment organisations are accredited by UKAS gives the confidence that they have been independently evaluated for their impartiality, competence and performance capability.

One of the responsibilities of UKAS is the accreditation of laboratories to issue NAMAS (National Accreditation of Measurement and Sampling) certificates and reports.

1.3.3 NAMAS

The NAMAS designation on a report or calibration gives the assurance that the work has been performed to the highest standards and that the laboratory has been stringently assessed by independent experts. There is further assurance that the work has been performed according to agreed methods and specifications and that all measurements are traceable to national and international standards.

A laboratory may apply to UKAS for accreditation with respect to specific tests or calibrations. The laboratory is assessed by UKAS for that specific work and if it meets NAMAS requirements, then the laboratory will be accredited for those areas of work and can then issue NAMAS reports and certificates. UKAS publishes the NAMAS Concise Directory that lists all accredited laboratories and services.

As part of the accreditation process, UKAS assesses all technical aspects of the laboratory's practices and organisation and not just the quality system. Typical areas of assessment would be:

- Organisation
- Quality system
- Quality audits and review
- Personnel
- Equipment
- Measurement traceability
- Methods and procedures
- Environment
- Sample handling
- Records
- Complaints
- Sub-contractors and purchasing.

This assessment is very similar to the assessment performed for ISO 9000 certification and laboratories meeting NAMAS requirements for calibration

and testing, where they are the supplier of these services, comply with the requirements of ISO 9002.

NAMAS accreditation is similar to the ISO 9000 certification process, in that it requires a thorough assessment by independently appointed industry experts. Six months following accreditation, a full follow-up visit is made by UKAS, and annual audits are made thereafter. Four years after accreditation a full re-accreditation assessment is made, although UKAS can make unannounced visits at any time. Laboratories found to be unsatisfactory on inspection will lose NAMAS accreditation until such time as that laboratory again meets the required standard.

NAMAS accreditation is an acceptable quality standard in a large number of countries both within the European Union and outside, and there exist a number of memoranda of understanding with these countries for mutual acceptance of standards.

Standards for the operation and accreditation of laboratories were originally set and published by the European Committee for Standardisation (CEN) in EN45001 and EN45002, (equating to ISO Guides 25 and 54) which were equivalent to the British standards, BS7500 series. The International Standard ISO/IEC 17025:1999 entitled *General requirements for the competence of testing and calibration laboratories* now replaces ISO/IEC Guide 25 and EN45001.

The pharmaceutical industry accepts a number of UKAS/NAMAS standards for a large variety of calibration and tests, although most companies would normally audit to confirm the acceptability of these standards in the case of very critical calibrations or tests.

1.4 Good laboratory practice (GLP)

1.4.1 Organisation for economic co-operation and development (OECD) GLP guide

The principles of GLP were originally developed under the auspices of the OECD and were first published in 1981 with later updates and guidance documents [7]. These principles are not legally binding but all OECD member countries have agreed to abide by them. However, the European Directive 87/18/EEC (amended by Commission Directive 1999/11/EC) requires that all EU member states must incorporate the OECD Principles of Good Laboratory Practice and Monitoring into national legislation. This has been accomplished in the UK as what is commonly known as The GLP Regulations [8]. In the USA, the GLP regulations have been incorporated into national law under Code of Federal Regulations (CFR) 21 part 58 and may be found on the FDA's web site [9].

1.4.2 Principles of GLP

The principles of GLP define a set of rules and criteria for a quality system concerned with the organisational process and the condition under which *non-clinical* health and environmental safety studies are planned, monitored, recorded, archived and reported. These principles have been developed to promote the quality and validity of data generated in the testing of chemicals. Apart from assuring the quality of data obtained from these studies that may have implication for human health, the other main advantage is the recognition by regulatory authorities of one country, of the data generated in other countries which hence avoids duplicative testing.

Any facility that produces data in support of these non-clinical studies is required to comply with the principles of GLP and will be audited for compliance by the appropriate regulatory authority. In the case of the UK this would be the United Kingdom GLP Compliance Monitoring Authority, which is part of the Department of Health. In the USA this would be the appropriate FDA department.

GLP must not be confused with that part of GMP that is concerned with operations in QC laboratories that assure the quality of medicines for human use (sometimes referred to as *good quality control laboratory practice*). Although there are a number of similarities in the practical aspects, GLP is in place to assure the integrity and quality of data; GMP is there to assure the quality of the product, i.e. its conformance to specification. There have been a number of statements recently from FDA sources on this subject [10].

- '(GLP)... is not the same as lab. work that tests finished drugs and active pharmaceutical ingredients. The GMP regulations have specific requirements for drug lab controls.'
- '.... manufacturers should not confuse good manufacturing practices (GMPs) with good laboratory practices (GLPs). The issue occasionally arises, as some firms confuse the terms.'
- 'It's a semantic issue.... but you can be sure there is no confusion at FDA. FDA does not care how a company refers to its practices. It cares about what those practices are.'
- 'While drug makers must account for many of the same issues in GMPs and GLPs, experts agreed, assessing quality and conformation to product specification is not the same as proving safety.'

One could of course argue that assurance of the integrity of data is also a requirement under any other quality system such as GMP. This assurance requires that analysts are trained, that procedures are written and approved, that analytical equipment is calibrated and maintained, that reagents and test materials are controlled and that accurate records and original raw data are kept.

1.5 Good manufacturing practice (GMP)

GMP is probably the most widespread quality system followed across the pharmaceutical industry as a whole. GMP compliance is a requirement within the R&D environment for the manufacture and testing of clinical trial materials (both drug product and API) and for commercial manufacture and testing of these materials for human and animal consumption. R&D facilities performing these operations may be subject to audit for compliance to GMP; commercial facilities *will* be audited by the appropriate regulatory authority, possibly without prior warning.

1.5.1 USA GMP regulations

The USA Food, Drugs and Cosmetics Act (FD&C Act) states that 'All drugs shall be manufactured, processed and packaged in accordance with current good manufacturing practice' [Section 501 (a)(2)(B)]. No distinction is drawn between the manufacture of drug products (secondary manufacture) and the manufacture of APIs (primary manufacture). It is also noted in the preamble to the FD&C Act that the act applies to all drugs for human use, and this therefore includes the requirement for both APIs and drug products manufactured for clinical trials, to be manufactured according to cGMP.

The requirements for compliance to cGMP are lain down in the following Code of Federal Regulations (21CFR):

Part 210 Current Good Manufacturing Practice in manufacturing, processing, packing or holding of drugs.
Part 211 Current Good Manufacturing Practice for finished pharmaceuticals.

It must be noted that the US regulations refer to *current* GMP. The regulations as detailed in 21CFR parts 210 and 211, give the pharmaceutical manufacturer plenty of scope to interpret the requirements appropriately for his specific facility and process, but in doing this the regulations require the manufacturer to adopt best *current* practice. The onus is placed upon the manufacturer to keep current with what the industry is doing (best practice), with what the current interpretation of the regulations are, and what the US FDA's expectations are.

Although the FD&C Act requires all drugs (products and APIs) to be manufactured to cGMP, the regulations 21CFR parts 210 and 211 are only mandatory for the manufacture of drug products and not APIs. In the past the onus has been on the pharmaceutical industry to interpret these requirements with respect to the manufacture of APIs. FDA has published guidelines in the form of guides for FDA investigators, to assist industry to meet compliance to cGMP and to place their interpretation on cGMP requirements for APIs and a number of other key areas such as impurities in new drugs, allowable solvent

residues and stability testing. Guides issued by ICH have now supplemented most of these guidelines and these, along with other FDA guidelines, will be discussed in more detail later in this chapter.

These regulations and guidelines may not always be appropriate for the manufacture of clinical trial materials. Although most of the regulations are reasonably applicable in an R&D drug product environment they may become inappropriate where attempts are made to apply them to the early manufacture of clinical APIs within an R&D environment. It is only with the issue of the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline ICH Q7A – *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* [3] in November 2000, that the worldwide pharmaceutical industry finally received detailed guidance for manufacture of APIs for both commercial and R&D purposes. (The scope and more detail of this guide will be discussed later.)

If one looks at the major headings of 21CFR part 211, the similarity with other quality systems becomes apparent. It is mandatory to have controls in the following areas:

Subpart A – General provisions
Subpart B – Organisation and personnel
Subpart C – Buildings and facilities
Subpart D – Equipment
Subpart E – Control of components and drug product containers and closures
Subpart F – Production and process controls
Subpart G – Packaging and labelling control
Subpart H – Holding and distribution
Subpart I – Laboratory controls
Subpart J – Records and reports
Subpart K – Returned and salvaged drug products.

The areas of these regulations that will be most important for a pharmaceutical analyst will be:

Organisation and personnel – this includes the requirement to have a QC unit having . . . responsibility and authority to approve and reject all components, drug product containers, closures, in-process materials, packaging materials, labelling and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. Further requirements cover laboratory facilities and the responsibility of the quality unit for approving or rejecting all materials, specifications and procedures. The responsibilities of the quality unit must be described in written procedures.

Laboratory controls – this part covers mainly calibration of equipment, testing and release procedures, stability testing, reserve samples, laboratory animals and penicillin contamination.

Records and reports – this part describes the key records that require to be retained. These include drug product component and container/closure records, labelling records, production records, production record review, laboratory records, distribution records and complaint files.

These requirements can be further compared with the ICH guidelines for API manufacture later in this chapter when I discuss worldwide harmonisation.

In conclusion, the USA cGMP regulations apply to interstate commerce within the USA and to any facility worldwide, that exports pharmaceutical materials (drug products, APIs, or components of these products) to the USA or, wishes to perform clinical trials in the USA. These facilities are open to inspection for cGMP compliance by US FDA inspectors and for those facilities found to be in non-compliance with these requirements the material will be deemed *adulterated with respect to identity, strength, quality and purity*. Products from these facilities will be refused entry for sell or use within the USA. Data from these facilities may not be accepted in support of regulatory filings.

1.5.2 EU/UK GMP requirements

Two European directives lay down the principles and guidelines for GMP in the EU, one for medicinal products for human use [11] and the other for veterinary products [12]. These directives have been incorporated in the national law of member states. The European Commission has issued nine volumes of *the rules governing medicinal products in the EU*. The latest edition was issued in 1998. Volume four covers GMP for medicinal products for human and veterinary use. These are now used as a basis for inspection by the various national regulatory authorities (e.g. Medicines Control Agency (MCA) in the UK).

If one looks at the requirement of the EU GMP rule, the similarity with 21CFR part 211 is clear, as is the consistency with other quality systems. The basic requirements are detailed under the following chapter headings:

Chapter 1: Quality assurance
Chapter 2: Personnel
Chapter 3: Premises and equipment
Chapter 4: Documentation
Chapter 5: Production
Chapter 6: Quality control
Chapter 7: Contract manufacture and analysis
Chapter 8: Complaints and recall
Chapter 9: Self-inspection

There are a further 14 Annexes:

Annex 1: Manufacture of sterile medicinal products
Annex 2: Manufacture of biological medicinal products for human use

Annex 3: Manufacture of radiopharmaceuticals
Annex 4: Manufacture of veterinary medicinal products other than immunologicals
Annex 5: Manufacture of immunological veterinary medicinal products
Annex 6: Manufacture of medicinal gases
Annex 7: Manufacture of herbal medicinal products
Annex 8: Sampling of starting and packaging materials
Annex 9: Manufacture of liquids, creams and ointments
Annex 10: Manufacture of pressurised metered dose aerosol preparations for inhalation
Annex 11: Computerised systems
Annex 12: Use of ionising radiation in the manufacture of medicinal products
Annex 13: Manufacture of investigational medicinal products
Annex 14: Manufacture of products derived from human blood or human plasma

1.5.3 USA/EU GMP differences

Historically there have been distinct and fundamental differences between USA regulation and EU/UK requirements for GMP. As discussed previously, the US required all *drugs* to be made to GMP requirements and performed inspections throughout the world in support of these requirements. In the UK, only drug products and biological manufacturers (not APIs, except some specified antibiotics) were inspected by the regulatory authority for compliance to GMP. Other EU countries, such as France and Italy, did require audits of API manufacturers, but the requirements and standards varied widely throughout the EU.

Although drug product manufacturers have always been audited by the UK authorities, the UK GMP guideline (The Orange Guide) was not mandatory and did not have the force of law. (Although non-compliance with GMP would result in non-approval of the facility to manufacture drug products for selling.) The original European Directive [13] defined a medicinal product as 'Any substance or combination of substances presented for treating or preventing disease in human beings or animals.' This applied to finished pharmaceutical dosage forms (drug products) only.

There are fundamental differences between a drug product and a *starting material* (API) that makes the application of many GMP drug product requirements difficult or inappropriate. An API is normally prepared by chemical processes that involve purification at each stage of manufacture, and early raw materials and processing stages may not have much influence over the quality of the final API. Impurities that are present in the final API will not be removed and will still be present in the manufacturer drug product. Similarly,