Regulatory aspects

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2.1 Introduction

The pharmaceutical industry is distinctive from many other industries in the amount of attention paid to it by regulatory authorities. In all industries there are regulations relating to safety and the environment, rules and directions for services and recommendations from a wide range of authorities about design and maintenance of facilities. Engineers in the pharmaceutical industry also have to cope with a myriad of medicines regulations throughout the design and engineering process. Whilst it is not essential to have a detailed knowledge of all aspects of the regulations of medicinal products, facilities and processes, engineers should at least recognize that many of these regulations are restrictive or impose additional requirements. When products and processes have been registered with the regulatory authorities, it can be difficult and time-consuming to alter these specifications. This makes it important to be aware of the registered processes and quality control systems throughout the design.

In the UK, medicines are regulated by the Medicines Control Agency (MCA). The MCA was launched as an Executive Agency of the UK Department of Health in July 1991. The MCA's primary objective is to safeguard public health by ensuring that all medicines on the UK market meet appropriate standards of safety, quality and efficacy. Safety aspects cover potential or actual harmful effects; quality relates to development and manufacture; and efficacy is a measure of the beneficial effect of the medicine on patients. The MCA operates a system of licensing before the marketing of medicines, monitoring of medicines and acting on safety concerns after they have been placed on the market, and checking standards of pharmaceutical manufacture and wholesaling. The MCA is responsible for enforcing these requirements. It represents UK pharmaceutical regulatory interests internationally; publishing quality standards for drug substances through the British Pharmacopoeia.

A medicinal product (also known as a drug product) is any substance or article that is administered for a medicinal purpose. This includes treating or preventing disease, diagnosing disease, contraception, anaesthesia and preventing or interfering with a normal physiological function.

In all cases, the product must be fit for the purpose for which it is intended. From the consumer's point of view this could be a single tablet, but each tablet cannot be tested to ensure it is of the correct quality as many of the tests needed to demonstrate this are destructive. Manufacturers have to assure quality by ensuring all aspects of the process are consistent every time.

As a result of well-publicized failures, resulting in patients deaths, regulations have become more and more stringent. Regulation is now achieved through the licensing of both the product and the facilities in which it is manufactured and the monitoring of medicines after a licence has been granted. The way medicinal products are supplied depends upon the nature and the historical experience of the product. Products may be Prescription Only Medicines (POM), Pharmacy only (P) or General Sales List (GSL). This categorization provides an important element in the control of medicinal products.

In the UK, the Medicines Act 1968 and the Poisons Act 1972, together with the Misuse of Drugs Act 1971, regulate all retail and wholesale dealings in medicines and poisons. Certain non-medicinal poisons and chemicals are also subject to the labelling requirements of the Chemicals Hazard Information and Packaging Regulations (CHIP).

It is important to appreciate at the outset that the Medicines Act 1968 applies only to substances where they are used as medicinal products or as ingredients in medicinal products.

2.2 Key stages in drug approval process

To obtain the evidence needed to show whether a drug is safe and effective, a pharmaceutical company will normally embark on a relatively lengthy process of drug evaluation and testing. Typically this will begin with studies of the drug in animals (preclinical studies) and then in humans (clinical studies). The purpose of preclinical testing is two-fold. Firstly, it is used as an aid to assessing whether initial human studies will be acceptably safe, and secondly, such studies are conducted to predict the therapeutic activity of the drug. If the drug looks promising, human clinical studies are proposed. In the USA, for example, this requires the submission of an Investigational New Drug Application (IND) to the regulatory authority, which in this case would be the Food and Drug Administration (FDA).

The IND must contain sufficient information about the investigational drug to show it is reasonably safe to begin human testing. An IND for a drug not previously tested in human subjects will normally include the results of

preclinical studies, the protocols for the planned human tests, and information on the composition, source and method of manufacture of the drug.

Provided the IND application is successful, drug testing in humans then proceeds progressively through three phases (called Phase 1, 2 and 3).

- Phase 1 includes the initial introduction of an investigational drug into humans and consists of short-term studies in a small number of healthy subjects, or patients with the target disease, to determine the metabolism and basic pharmacological and toxicological properties of the drug, and if possible, to obtain preliminary evidence of effectiveness.
- Phase 2 consists of larger, more detailed studies; usually including the first controlled clinical studies intended to assess the effectiveness of the drug and to determine the common short-term side effects and risks of the drug.
- Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence of effectiveness has been established and are designed to gather the additional information necessary to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for professional labelling.

If the results appear to be favourable at the end of clinical trials and the company decides to market the new product, they must first submit an application to do this. In the USA the company must submit the results of the investigational studies to the FDA in the form of a New Drug Application (NDA). The NDA must contain:

- full reports of the studies (both preclinical and clinical) to demonstrate the safety and effectiveness of the drug;
- a description of the components, chemical formulation, and manufacturing controls;
- samples of the drug itself and of the proposed labelling.

Many companies choose to prepare a Drug Master File (DMF) to support the NDA. A DMF is submitted to the FDA to provide detailed information about facilities, processes or articles used in the manufacturing, processing, packaging and storage of one or more human drugs. In exceptional cases, a DMF may also be used to provide animal or clinical data. A DMF is submitted solely at the discretion of the holder, the information being used in support of the NDA.

The application is reviewed. Typically this includes reviews of product chemistry, labelling, bio-equivalency, clinical data and toxicity. In addition, and of particular relevance to pharmaceutical engineers, the review will also include a pre-approval inspection of the facilities in which the drug is manufactured.

The pre-approval inspection will generally consist of a review of the facilities, procedures, validation (discussed in Chapter 4) and controls associated with formulation development, analytical method development, clinical trial manufacturing, manufacturing (if applicable), quality control laboratories, bulk chemical sources and contract operations. If the application is successful the pharmaceutical company will receive approval to market the product.

A similar (although not identical) situation exists in Europe. For example, in the UK regulation is achieved through a Clinical Trial Certificate, Animal Test Certificate and Product Licence (also in certain circumstances Product Licence of Right and Reviewed Product Licence) for the product and a Manufacturer's Licence, Assembly Only Licence, Special Manufacturer's Licence, Wholesale Licence and Wholesale Import Licence for the Manufacturer/Supplier.

2.3 Example of requirements

An example of the 'regulatory environment' in the UK is summarized in Figure 2.1:

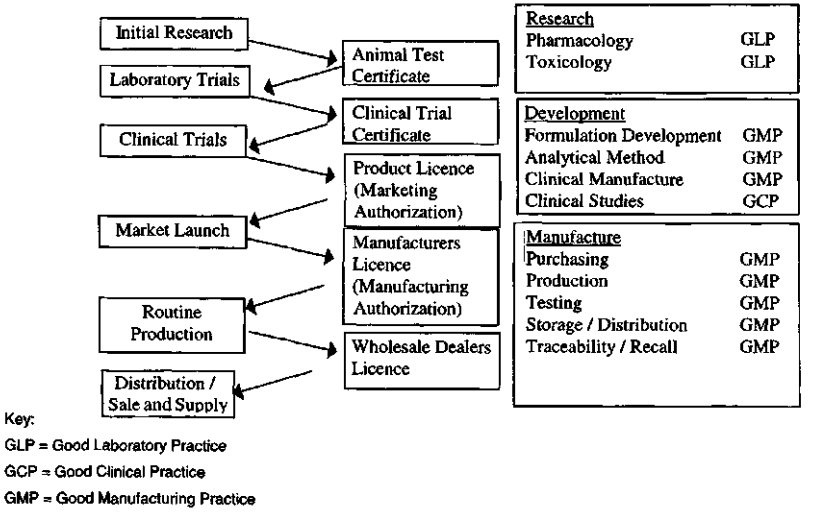

Figure 2.1: The UK regulatory environment

GLP is concerned with the organizational processes and the conditions under which laboratory studies are planned, performed, monitored, reported and recorded. The UK GLP regulations (Statutory Instruments No. 654) came into force in April 1997 and are monitored by the UK GLP Monitoring

Authority, which is part of the MCA. Currently about 150 test facilities are registered under the scheme and are inspected on a two-year cycle.

GCP is 'a standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials that provide assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected' (Definition from the International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)). In the UK, the GCP Compliance Unit was established within the Inspection and Enforcement Division of the MCA in 1996. GCP inspectors assess compliance with the requirements of GCP guidelines and regulations, which involves conducting on-site inspections at pharmaceutical sponsor companies, contract research organizations' investigational sites and other facilities involved in clinical research.

GMP is 'the part of Quality Assurance (QA) which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by marketing authorization or product specification.' (Definition from the EU Guide To Good Manufacturing Practice and Good Distribution Practice). GMP is discussed in more detail in Chapter 3.

2.4 Post-marketing evaluation

2.4.1 Pharmacovigilance

No matter how extensive the pre-clinical work in animals and clinical trials in patients, certain adverse effects may not be detected until a very large number of people have received the new drug product. The conditions under which patients are studied pre-marketing do not necessarily reflect the way the new drug product will be used in hospitals or in general practice. Pharmacovigilance is the process of monitoring medicines as used in everyday practice to:

- identify previously unrecognized (or changes in) patterns of adverse effects;
- assess the risks and benefits of medicines in order to determine what action, if any, is necessary to improve their safe use;
- provide information to users to optimize safe and effective use of medicines;
- monitor the impact of any action taken.

Information from many different sources is used for pharmacovigilance including spontaneous adverse drug reaction (ADR) reporting schemes, clinical and epidemiological studies, world literature, morbidity and mortality

databases. In the UK the MCA runs the spontaneous adverse drug reaction reporting scheme (called the Yellow Card Reporting Scheme) which receives reports of suspected drug reactions from doctors, dentists, hospital pharmacists and coroners. The scheme provides an early warning of adverse effects of medicines.

2.4.2 Variations and renewal of marketing authorizations

Drug products may undergo changes over time in relation to production, distribution and use. These will require authorization by the licensing agency. Also, authorizations are normally renewed on a regular period — marketing authorizations are valid for five years in the UK.

2.5 Procedures for authorizing medicinal products in the European Union

In 1995 a new European system for the authorization of medicinal products came into effect, and a new agency was established — the European Medicines Evaluation Agency (EMEA) based in London, UK. Two new registration procedures for human and veterinarian medicinal products have become available. The first system, known as the centralized procedure, is compulsory for medicinal products derived from biotechnology and is available at the request of companies for other innovative new products. Applications are submitted directly to the EMEA who undertake the evaluation and submit their opinion to the European Commission. The European Commission then issue a single market authorization.

The second system, known as the decentralized procedure, applies to the majority of conventional medicinal products and is based upon the principal of mutual recognition of national authorizations. It provides for the extension of the marketing authorization granted by one Member State to one or more other Member States identified by the applicant.

2.6 European and US regulatory perspectives

On the 18 May 1998, the European Union and the USA signed a 'Joint Declaration to the agreement on Mutual Recognition between the EU and the USA'. This agreement lays down the framework for mutual recognition of GMP regulations under the principal of 'equivalence' and the mutual recognition of pre-approval and post-approval inspections.

The agreement covers human medicinal products (prescription and non-prescription drugs, biologicals including vaccines and immunologicals); veterinary pharmaceuticals (prescription and non-prescription drugs premixes and preparations for medicated feeds); active pharmaceutical ingredients and intermediate product, starting materials, bulk pharmaceuticals. The agreement excludes human blood, human plasma, human tissues and organs, veterinary immunologicals, human plasma derivatives, investigational medicinal products, human radiopharmaceuticals and medicinal gases.

Reading list

1. Rules and guidance for pharmaceutical manufacturers and distributors 1997. London. The Stationery Office, 1997. ISBN 0 11 321995 4. (Also known as the 'Orange Guide'). (Incorporating EC Guides to Good Manufacturing Practice and Good Distribution Practice; EC GMP Directives (91/356/EEC & 91/412/EEC); Code of Practice for Qualified Persons and Guidance for Responsible Persons; Standard provisions for manufacturer's licences; Standard provisions for wholesale dealers licences; Guidance on reporting defective medicines).
2. Good Laboratory Practice Regulations 1999 (GLP Regulations); Statutory Instrument 1999/3106; Department of Health, The United Kingdom Good Laboratory Practice Monitoring Authority.
3. Guide to UK GLP Regulations 1999, Feb 2000, Department of Health, The United Kingdom Good Laboratory Practice Monitoring Authority.
4. International Conference on Harmonization (ICH) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
5. Research Governance in the NHS, Guidance on Good Clinical Practice and Clinical Trials in the NHS, Department of Health
6. Royal Pharmaceutical Society of Great Britain; Medicines, Ethics and Practices, A guide for Pharmacists, 18 Edition, July 1997.
7. US Food and Drug Administration, Centre for Drug Evaluation and Research (CDER), Department of Health and Human Services; Code of Federal Regulations 21 CFR (in particular, but not limited to, Parts 10b, 11, 210, 211, 600, 820). Guidance for Industry, including: Guideline For Drug Master Files September 1989; Content and format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic Biotechnology-derived Products; Guideline for the Format and Content of the Microbiological Section of An Application (Docket No. 85D-0245); February 1987; Guideline for the Format and Content of the Chemistry, Manufacturing and Controls Section of An Application; Preparing Data for Electronic Submission in ANDAs [HTML] or [PDF], Sep 1999; Regulatory Submissions in Electronic Format; General Considerations Jan 1999; Regulatory Submissions in Electronic Format; New Drug Applications Jan 1999.

8. Agreement on Mutual Recognition between the European Community and the United States; US – EC MRA Pharmaceutical Good Manufacturing Practice Annexe; Sectorial Annex For Pharmaceutical Good Manufacturing Practice; Signed 18 May 1998; Exchange of Letters 30 October 1998; Published in Official Journal L 31, 4 February 1999

Web Sites

www.fda.gov/cder/guidance/index.htm
www.emea.eu.int/
www.mca.gov.uk
www.rpsgb.org.uk/