10

Licensing of drugs and the *British Pharmacopoeia*

The licensing of drugs and medicines in the UK is carried out by the Medicines and Healthcare products Regulatory Agency (MHRA), an executive agency of the Department of Health, from their offices in central London. The MHRA is charged by government to ensure that medicines and medical devices work and are acceptably safe. The scope of products regulated by MHRA is vast and includes:

- **Medicines**, which are defined as any products or preparations used to prevent, treat or diagnose disease (including anaesthesia). All new medicines must satisfy the MHRA in terms of *safety, quality* and *efficacy*.
- **Medical devices**, which are all products, except medicines, used in healthcare for the diagnosis, prevention, monitoring or treatment of illness or disability and can include anaesthetic equipment, dressings, catheters, endoscopes, thermometers, syringes and needles as well as larger equipment such as ventilators, defibrillators and wheelchairs.
- **Tissue engineering**, describes products which are derived from cells and tissues. These may be *autologous* if derived from the patient's own cells and used to treat that patient or *allogeneic* if derived from the cells of one person to be used in the treatment of another.
- **Nanotechnology**, which is a general term for developments in many different fields including engineering, chemical synthesis and electronics. The *nanoscale* is defined as representing all materials from approximately 100 nm (100×10^{-9} metres) in size down to objects less than 1 nm. At this very small scale, subtle changes in the structure of a material can greatly affect the physicochemical properties the material possesses. Examples of medical devices within the nanoscale are surgical implants, dental and orthopaedic prostheses and incredibly small surgical instruments able to carry out microsurgery within individual cells.
- **Blood products**, which include whole human blood for use in transfusion as well as blood-derived products such as clotting factors, proteins, etc. The term *haemovigilance* is used to describe the surveillance procedures adopted to monitor serious adverse or unexpected events related to products derived from blood.

Structure of the MHRA

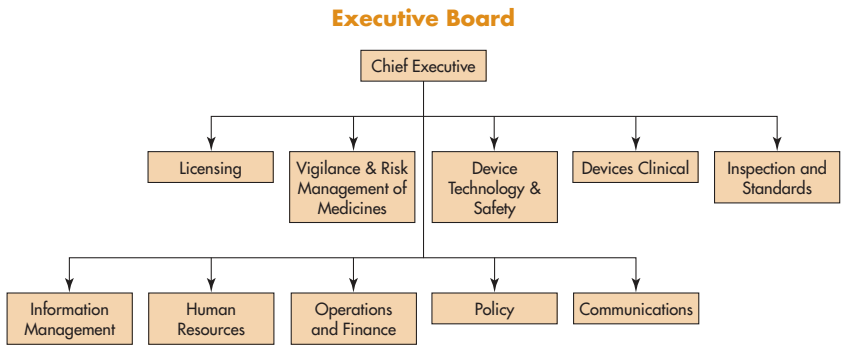


Figure 10.1 The structure of the MHRA.

To achieve all of the tasks described above, the MHRA is organised into a number of organisational divisions each responsible for one aspect of the overall role. There are ten divisions in all, including *Inspection and Standards Division* which ensures compliance with the standards that apply to the manufacture and supply of medicines on the UK market; *Licensing Division*, responsible for assessing and approving applications for marketing authorisations for new medicinal products, new routes of administration or new formulations for existing drugs; and *Vigilance and Risk Management of Medicines Division*, whose objective is to protect public health by promoting the safe use of marketed medicines. In addition to these key roles there are a number of ancillary divisions responsible for matters such as Communications, Policy, Finance and Human Resources. A complete description of the internal organisation of the MHRA is outside the scope of this book but detailed information may be obtained from the MHRA webpage at www.mhra.gov.uk.

European Licensing Procedures

Since the first European Directive on medicinal products was published in 1965, a lot of work has been done to harmonise the authorisation of medicinal products across the European Union (EU). At the time of writing (early 2007) the most recent legislation is Directive 2001/83 implemented in October 2005.

There are essentially two types of European licensing procedures:

- the *Centralised Procedure (CP)* and the
- *Mutual Recognition (MRP)* or *Decentralised Procedure (DCP)*.

The Centralised Procedure results in a single application, a single evaluation and a single authorisation in all member states of the EU and generates a European marketing number for the product.

The Centralised Procedure is **mandatory** for certain categories of product such as

(a) medicinal products for the treatment of AIDS, cancer, neurodegenerative diseases or diabetes
(b) biotechnology products such as monoclonal antibodies or gene therapy
(c) products designed to treat very rare diseases such as nephropathic cystinosis, porphyria or Wilson disease (the so-called 'orphan' medicinal products).

The Centralised Procedure is **optional** for

(a) new active substances not currently authorised in the EU
(b) therapeutically innovative products, e.g. medicinal products utilising a novel delivery method or specialised novel formulation (such as an iontophoretic device)
(c) generic medicinal products or products intended for OTC use.

In the Centralised Procedure a Rapporteur and a Co-Rapporteur, appointed from within the member states of EU, have to evaluate the product and report to the European Medicines Agency within 210 days. If the UK is selected as Rapporteur or Co-Rapporteur, the evaluation of the medicinal product is carried out by the MHRA. Occasionally, when there is particular interest in a novel medicinal product, or when a new medicinal product would have a significant affect on drug usage in the NHS, the MHRA will get involved and opinions will be sought from scientific advisory committees. A recent example of this was when the first inhaled formulation of human insulin was licensed.

The Mutual Recognition Procedure has been in place for many years and may be used for all medicinal products except those derived from advances in biotechnology, which have to go through CP. The basis of the MRP is that if a marketing authorisation for a product is granted in one member state of the EU, the applicant may then apply to be 'mutually recognised' in any number of other states. Under this procedure, member states are obliged to approve the marketing authorisation of the novel medicinal product within 90 days of application, unless they can prove a serious risk to public health, in which case the approval will not be granted. Problems with this procedure can arise due to the relatively short time allowed for approval.

The Decentralised Procedure was introduced in 2001 as an attempt to streamline (and speed up!) the licensing process. The DCP may be used when a medicinal product has not received a marketing authorisation in any

member state of the EU. Under the DCP, dossiers of evidence are submitted to all member states simultaneously and one state is chosen as the reference member state. The reference state conducts a full assessment of the proposal, which is sent to the other states by day 70 of the process. Again, time is short and the MHRA often has to move quickly to complete an evaluation of the product application.

Applications for Marketing Authorisations

The amount of scientific information contained in a licensing application may be vast (often exceeding 1000 pages). The pharmaceutical company presents evidence to show that every aspect of production of the medicinal product has been controlled and validated and is of an acceptable quality. The application starts with a description of the discovery chemistry for the new drug. This may be a chemical synthesis or an extraction of an active natural product from a plant or microorganism. Spectroscopic (e.g. NMR, MS, IR) and chromatographic (e.g. HPLC, GC) data are presented to show that the correct compound has been synthesised, and that by-products are identified and their levels controlled. The new chemical entity is then subjected to stability testing under accelerated conditions of heat, humidity, etc. to calculate shelf-life and rates of decomposition. Each decomposition product is identified and any potential toxicity is controlled.

A large section of the application concerns the formulation of the new drug into a medicine suitable for use by the patient. Pharmaceutical processes such as milling, sieving, tabletting, micronisation, freeze drying, etc. are described and data are presented to show compliance. Further studies are then carried out on the finished medicinal dosage form, such as dissolution, disintegration, particle sizing, detection of polymorphism, etc.

The third section of an application usually contains clinical data. This may take the form of pharmacokinetic studies in both animals and human volunteers. Measurements such as plasma levels, area under the curve, protein binding, etc. are compared with data from other manufacturer's products and conclusions are reached about the safety, quality and efficacy of the new product.

The final section of the application usually contains data on the patient information leaflet (PIL), labelling, instructions for use and packaging of the final product. These data are read carefully to ensure the patient receives clear and unambiguous information.

Applications for licensing are considered by assessors at the MHRA. In arriving at a decision, the assessors may take independent advice on matters such as safety, quality and efficacy from medicine advisory bodies

such as the Commission on Human Medicines. These bodies consist of independent members who are appointed by Ministers and are not staff of MHRA. Not all applications for a Marketing Authorisation are successful; the drug company may be asked to undertake further studies, or provide additional data to support their application. Occasionally, an application may fall due to serious issues relating to public health.

British Pharmacopoeia Commission

The British Pharmacopoeia Commission was established in 1970 under Section 4 of the Medicines Act 1968. Members of the Commission (approximately 20) are appointed by the Minister of Health and are responsible for preparing new editions of the *British Pharmacopoeia* (BP) and the *British Pharmacopoeia* (*Veterinary*). The Commission also provides members for the UK delegation to meetings of the European Pharmacopoeia committees in Strasbourg and is responsible, under Section 100 of the Medicines Act, for selecting and advising on British Approved Names (BANs).

To help the Commission in its work, a number of Expert Advisory Groups (EAGs) have been established. The EAGs function as committees of the Commission and meet approximately four times a year; these are the meetings where new monographs are planned and prepared and where the 'nitty gritty' of the Pharmacopoeia is discussed. There are EAGs covering areas such as Medicinal Chemicals, Pharmacy, Herbal and Complementary Medicines, Microbiology, Biological and Biotechnological Products, and Veterinary Products. Each EAG is chaired by a member of the Commission and is composed of experts in the relevant field.

The BP Commission can also call on expertise available in the British Pharmacopoeia laboratories situated in the premises of the Laboratory of the Government Chemist in West London. The BP laboratory carries out and validates assay procedures for the Commission and in addition, is responsible for the procurement, establishment, maintenance and sale of British Pharmacopoeia Chemical Reference Substances (BPCRS). These reference substances, as their name suggests, are authentic samples of a drug or decomposition product which are used as standards in a drug assay. The BP laboratory also fulfils an important forensic role in the control of counterfeit medicines. With the advent of the internet, the public can easily gain access to supplies of prescription-only medicines online. These medicines are often adulterated, contaminated or simply counterfeit, and comparison with authentic samples is necessary to ensure that the correct preparation is supplied.

The *British Pharmacopoeia*

The *British Pharmacopoeia* (BP) is a substantial document which contributes to overall control of the quality of medicinal products by providing an authoritative statement of the quality a product is expected to achieve at any time during its period of use. The standards of the BP are publicly available, legally enforceable and are designed to complement and assist the UK licensing and inspection processes.

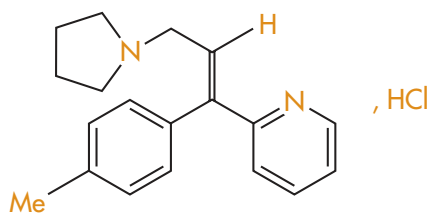
The book itself comprises:

Volumes I and II	Monographs of Medicinal Substances, arranged alphabetically
Volume III	Formulated Preparations, Blood, Radiopharmaceutical and Immunological Products
Volume IV	Appendices (reagents, analytical techniques, etc), IR spectra, Index
Volume V	BP (Vet)
Volume VI	CD-ROM version and list of British Approved Names

There is also a searchable online version of the text available at http://www.pharmacopoeia.org.uk/

As was stated in Chapter 6, each substance in the British Pharmacopoeia is given a specific *monograph*, which lists the chemical structure of the compound (if known), the definition and statement of BP limits (quoted to one decimal place), a description of its characteristics (colour, solubility, etc.), some tests for identification of a sample of the material and limit tests for impurities. The monograph ends with the official BP assay for determination of purity and the chemical structures of known impurities which may be present as by-products of the synthesis or decomposition products formed on storage. Formulated medicines may have, in addition to a specific monograph, a *general monograph*, which applies to that class of medicine (tablets, suspensions, etc.). Importantly, the letters 'BP' after the name of the medicine imply compliance with both the requirements of the specific monograph for the drug and the requirements of the general monograph for the medicine. A sample monograph for Triprolidine Hydrochloride is reproduced below.

(Ph Eur monograph 0968)



$C_{19}H_{22}N_2,HCl,H_2O$ 332.9 *6138–79–0*

Action and use
Histamine H_1-receptor antagonist

Preparations
Triprolidine Tablets

DEFINITION
Triprolidine Hydrochloride is (*E*)-2-(3-pyrrolidin-1-yl-1-*p*-tolylprop 1-enyl)-pyridine hydrochloride monophydrate. It contains not less than 98.5% and not more that 101.0% of $C_{19}H_{22}N_2,HCl$, calculated with reference to the anhydrous substance.

CHARACTERISTICS
A white, crystalline powder. Freely soluble in *water*; freely soluble in *ethanol (96%)* and practically insoluble in *ether*.

IDENTIFICATION
A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of triprolidine hydrochloride *(RS 356)*.
B. Yields reaction A characteristic of *chlorides*, Appendix VI.

TESTS
Related substances
Carry out the method for *thin-layer chromatography*, Appendix III A, using a silica gel F_{254} precoated plate (Merck silica gel 60 F_{254} plates are suitable) and a mixture of equal volumes of *butan-2-one* and *dimethylformamide* as the mobile phase. Apply separately to the plate 5 µl of each of three solutions in *methanol* containing (1) 1.0% w/v of the substance being examined, (2) 0.020% w/v of *Z-triprolidine hydrochloride BPCRS* and (3) 0.010% w/v of the substance being examined. After removal of the plate, allow it to dry in air and examine under *ultraviolet light (254 nm)*. In the chromatogram obtained with solution (1) any spot corresponding to *Z*-triprolidine is not more intense than the spot in the chromatogram obtained with solution (2) and any other *secondary spot* is not more intense than the spot in the chromatogram obtained with solution (3).

Sulphated ash
Not more than 0.1%, Appendix IX A.

Water
4.5 to 6.0% w/w, Appendix IX C. Use 0.4 g.

ASSAY
Carry out Method I for *non-aqueous titration*, Appendix VIII A, using 0.25 g dissolved in a mixture of 50 ml of *anhydrous acetic acid* and 0.5 ml of *acetic anhydride* and *crystal violet solution* as indicator. Each ml of 0.1M *perchloric acid VS* is equivalent to 15.74 mg of $C_{19}H_{22}N_2$,HCl.

In addition to the monographs, the BP contains a section on *General Notices,* printed at the beginning of each volume on coloured paper. These notices include important definitions (e.g. recently prepared), and data on subjects such as solubility (freely, sparingly, etc.), storage conditions, labelling requirements, chemical formulae, as well as cross references to the *European Pharmacopoeia* (EP) produced in Strasbourg.

Two of the most important sections of the BP are found in Volume IV. These are the tables of IR spectra and the Appendices. IR spectra are included to allow comparison of authentic samples with unknown samples or samples which may be contaminated with impurities. As was stated in Chapter 7, two compounds may be considered identical if their IR spectra, obtained under identical conditions, coincide completely – i.e. the same peaks are present in the same positions with the same intensities. The BP also describes the equipment to be used and conditions to be followed to obtain the spectra.

The Appendices of the BP contain a host of useful information and time spent on their study is rarely wasted. Appendix I lists the specifications of the general reagents used in Pharmacopoeia assays. These include solvents such as ethanol, acetone, etc., reagents such as silica gel for chromatography and essential laboratory reagents such as buffers and indicators for titrations. Appendix II contains information on spectroscopy (IR, UV, NMR, AA and AE) as well as mass spectrometry and less well known analytical techniques such as X-ray fluorescence and Raman spectroscopy. Appendix III is concerned with chromatographic separation techniques including thin-layer (TLC), gas (GC) and high-performance liquid chromatography (HPLC). There are also descriptions of related techniques such as capillary electrophoresis (CE) and details on amino acid analysis and peptide mapping.

The rest of the appendices (which go up to Appendix XXV) are concerned with descriptions of physical techniques such as determinations of melting, freezing and boiling points, viscosity, thermal analysis, conduc-

tivity of solutions, determination of gases, proteins, pesticide residues, and so on.

Finally, a number of Supplementary Chapters describe important topics such as endotoxin testing, statistical analysis of experimental results and guides for the nomenclature of complex natural or semi-synthetic drugs. Supplementary Chapter III F describes the validation of analytical procedures and contains a glossary of terms and their definitions, such as *specificity*, *accuracy*, *precision*, *detection limit*, etc.

A full description of the huge amounts of information available is outside the scope of the present text and the interested reader is encouraged to consult the BP directly. Undergraduate students, in particular, should be aware of the vast amount of useful and relevant information contained within the Pharmacopoeia.

At the time of writing, the BP Commission is grappling with problems associated with control of material for use in homeopathic medicine. In homeopathy, a medicinal product is considered to become more potent when it is diluted with inert material. This somewhat counter-intuitive method of manufacture results in homeopathic preparations which contain not a single molecule of the original drug (i.e. the preparation has been diluted beyond the Avogadro number, 6.02×10^{23}). Preparations of this type clearly present a challenge for the pharmaceutical analyst charged with ensuring compliance with BP requirements! The best that can be done is to ensure that the stock material from which the homeopathic preparation is prepared, which may be a conventional drug or a herbal product, is of Pharmacopoeia quality.

Other pharmaceutical challenges, such as how to label and dispense a preparation containing nothing but solvent, are (thankfully) beyond the scope of the present text.