Chapter 11

The Rules Governing Medicinal Products for Human Use in the European Union

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11.1 European Economic Council Directives and Regulations

The peaceful application of nuclear reactors after World War II initiated the production of large quantities of radionuclides, which were introduced to medicine for the investigation of human physiology and disease. The application of radioactive tracers for clinical diagnosis and therapy increased by the year, resulting in the widespread use of radioisotopes in clinical procedures.

Radioactivity has been the concern of physicists, who set up rules and regulations for the protection of the general public and health personnel handling radioactive materials. At most institutions, the commercially available radiopharmaceuticals were managed by a responsible staff of health physicists.

In some European countries, the distribution of radioactive compounds to the users was considered the responsibility of the pharmacist. The first centralized isotope pharmacy was installed in Denmark, taking responsibility for the quality and distribution of radioactive drugs since 1976. Different combinations of primary legislation for non-radioactive drugs (i.e., the Medicines Act) and national administrative arrangements provided legislation for consumer protection regulating the importation, manufacture, and sale or supply of radioactive medicinal products (Appendix A.2).

Requirements for good radiopharmacy practice and specific guidelines for simple procedures such as handling of ready-for-use radiopharmaceuticals and the preparation of $^{99mTc}$-labeled radiopharmaceuticals from generators and kits were presented in a comprehensive report by Kristensen (1979) based on existing good manufacturing practice (GMP) recommendations and standards applied to the manufacture of pharmaceuticals (Appendix A.3). The demand on qualified personnel, and premises for small-scale production in a radiopharmacy posed a considerable challenge.

The European regulatory bodies have three main instruments to reach an approximation of national regulations: directives, guidelines, and European regulations.

- **Directives** are rules addressed to the member states to be translated into the respective national legislation and effectively implemented. Directives are mandatory.
- **Guidelines** are recommendations for the effective implementation of directives by the member states. Guidelines are not mandatory.
- The **European regulations** are mandatory in all European Union countries; they are applied into the national legislation without translation.

In 1989, the European Economic Council issued Directive 89/343/EEC as an amendment to Directive 75/319/EEC, which, for the first time, defines different classes of radiopharmaceutical products and states the requirements for marketing authorization of these products as proprietary medicinal products for human use (Appendix A.1). Implementation of directives into national law provides legislation that is effective in all member states, resulting in a harmonization within the European Union.
The comprehensive legislation regulating all medicinal products in the European Union is organized in seven volumes in *The Rules Governing Medicinal Products in the European Union*:

- Volume 1 contains the directives governing medicinal products for human use in the European Union.
- Volume 2 contains the notice to applicants for marketing authorization of medicinal products.
- Volume 3 contains the guidelines concerning quality, safety, and efficacy.
- Volume 4 contains pharmaceutical legislation of GMP for the manufacture of medicinal products.
- Volumes 2, 3, and 4 present specific guidelines for radiopharmaceutical products.
- Volumes 5, 6, and 7 are dedicated to medicinal products for veterinary use.

Council directives relating to marketing authorization of medicinal products for human use and amending texts are listed in Volume 2B (annex).

Some directives relevant for radiopharmaceuticals as medicinal products are discussed here in chronological order.

Directive 65/65/EEC is the basis of all pharmaceutical regulations. It includes relevant definitions (medicinal product, proprietary medicinal product, officinal and magisterial formula, etc.) and states the registration by law for all proprietary medicinal products. Since 1965, this directive has been amended several times.

Directives 75/318/EEC and 75/319/EEC, amended at different times from the original version, state the documents and requirements for manufacture and marketing authorization. Definition of the professional profile of the qualified person responsible for the quality of medicinal products is presented, and a technical body on medicines, the Committee of Proprietary Medicinal Products (CPMP), is created. Due to technical reasons, some products such as vaccines and sera, homeopathics, hemoderivatives, and radiopharmaceuticals were excluded from the scope of this directive in its original version.

In 1987, Directive 87/22/EEC created the centralized marketing authorization of medicines, particularly those derived from biotechnology in accordance with the CPMP, as a valid procedure for drug registration in all member states. This centralized procedure should be applied to relevant new medicinal products, such as those obtained by biotechnology, monoclonal antibodies, or radionuclides. Therefore, radioactive medicinal products were recognized in this context as drugs, requiring the modification of Directives 65/65/EEC, 75/318/EEC and 75/319/EEC to extend their provisions to the products previously excluded; this amendment was introduced by Directive 89/341/EEC.

After Directive 89/341/EEC had been issued, a block of directives, so-called extension directives, extended the scope of Directives 65/65/EEC, and 75/319/EEC to vaccines and sera, homeopathics, hemoderivatives, and radiopharmaceuticals, giving specific details for them. This means that all pharmaceutical directives must be applied to these products.

One of these extension directives is 89/343/EEC, extending the scope of the pharmaceutical directives to radiopharmaceuticals, defining all radiopharmaceutical products (radiopharmaceuticals ready for use, cold kits, generators, and radionuclide precursors) as drugs for which marketing authorization as proprietary medicinal products for human use is required. However, this authorization shall not be required for radiopharmaceuticals prepared at the time of use, if prepared by using authorized products (cold kits, generators, and radionuclide precursors) and in accordance with the instructions given by the manufacturer. This directive does not derogate in any way the rules on radiation protection.