

Pharmaceutical regulation covers the entire life cycle of a medicine

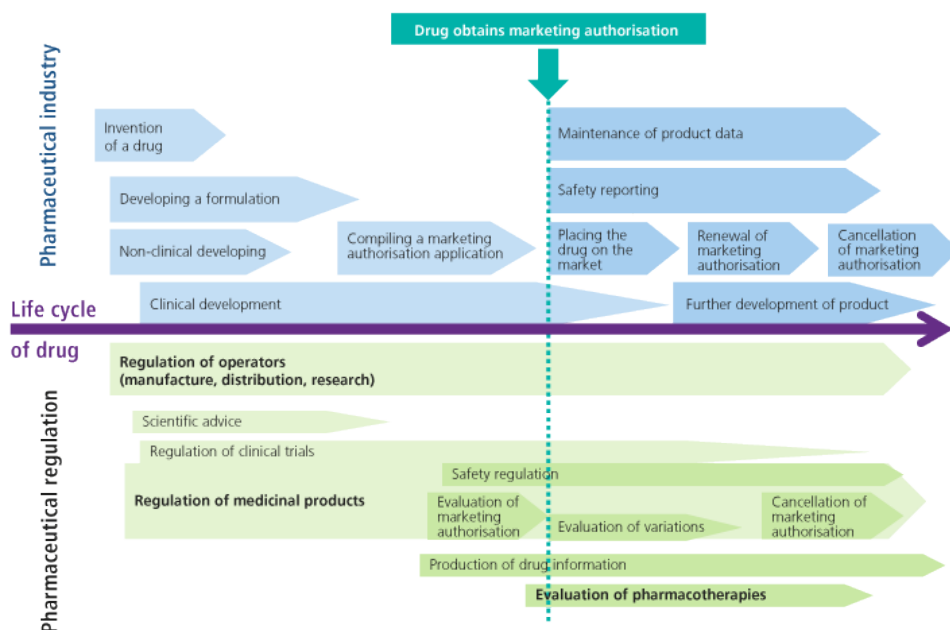
The objective of pharmaceutical regulation is to maintain and promote the safety of medicines and their use as well as ensuring appropriate manufacture and availability of drugs. The regulation covers the entire life cycle of a medicine, starting from preclinical trials and manufacture of an investigational drug down to the point when the drug exits the market.

For historic reasons, the role of authorities in pharmaceutical regulation is far more prominent than in the regulation of the majority of other instruments employed in health care. The system of marketing authorisation for medicines was introduced in the United States in the autumn of 1937 as a sequel to an incidence where one hundred people died from kidney failure induced by Elixir Sulfanilamide that contained diethylene glycol. The thalidomide catastrophe of 1961 resulted in the establishment in most industrialised countries of the marketing authorisation procedure, reporting systems on adverse reactions, and registers of congenital malformations. In Finland, the marketing authorisation procedure was started in 1964 and maintenance of the adverse reaction database in 1966.

On the basis of the life cycle of a drug, pharmaceutical regulation can be roughly divided into pre-marketing control and post-marketing control, the demarcation point being the marketing authorisation for the drug (figure 1). The main objective of pre-marketing control is to ensure that, upon the granting of marketing authorisation, drugs have an acceptable benefit-to-risk ratio. Regulation of the different research phases and manufacture is in turn necessary so that the research results and the conclusions drawn from them can be considered reliable. This ensures the comparability of the medicinal product on sale on the one hand and the product used in the research – demonstrating the efficacy and safety of the drug – on the other.

The majority of the legislative framework pertaining to pharmaceutical regulation that is valid in Finland is part of the EU's harmonised legislation. Only the provisions pertaining to retail distribution are purely national.

Figure 1. How pharmaceutical regulation is related to the life cycle of a drug.



Regulation begins prior to marketing authorisation

As early as in the preclinical testing phase of a drug, regulatory control begins when safety studies on a novel drug candidate are initiated: preclinical safety studies must be performed in compliance with GLP (Good Laboratory Practice) in a GLP-certified laboratory.

Permission for clinical trials must be obtained from the Ethical Committee. Furthermore, advance notice of such trials must be given to Fimea, who can then request further clarification or decline the start of the trial. In Finland, 150–200 notices are submitted annually, all of them being processed nationally. Test results and adverse reactions found in the tests are also reported to Fimea.

Marketing authorisation can be obtained in several ways

A drug may only be sold if it has marketing authorisation or a special permission for compassionate use, or an exemption has been granted so as to release it for consumption. The majority of novel drug inventions obtain their marketing authorisation in the EU via what is known as the centralised marketing authorisation procedure, in which the EU Commission decides on a marketing authorisation for the territory of the entire Union on the basis of an opinion issued by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). CHMP comprises delegates from all Member States, and the actual evaluation of an application is carried out by expert teams formed by the CHMP delegates chosen as Rapporteur and Co-Rapporteur in each individual case from the agencies of their home

countries.

Marketing authorisation in the EU can also be applied for directly from the medicines agency of a Member State. In Finland, such purely national marketing authorisation applications have become scarce: only a dozen are filed annually.

The major route for marketing authorisations for generic medicines is the decentralised marketing authorisation procedure, in which a company applying for marketing authorisation submits an application in several Member States of the EU at the same time and simultaneously requests the agency of one Member State to serve as the actual evaluating country, i.e. the Reference Member State, for the application. The assessment report issued by this Reference Member State can then be commented on by the Member States participating in the procedure on an agreed schedule. The procedure will result in a marketing authorisation that is uniform in all participating Member States but granted nationally by the authority of each Member State.

It is also possible to expand the marketing authorisation granted in one EU country to the others in what is known as the mutual recognition procedure, in which a Member State that has already granted marketing authorisation serves as a Reference Member State. In this procedure, the participating Member States have an opportunity, similar to that in the decentralised procedure, to influence the content of the authorisation decision resulting from the process. In this case, the final result is also a uniform marketing authorisation granted by the authority of each Member State.

The authorisation procedure is governed by criteria for efficacy, safety and acceptable quality as well carefully mapped practices that are uniform within the EU.

Risk management

A new drug that has obtained marketing authorisation has usually been tested on a maximum of a few thousand patients. Scant information therefore exists on rare adverse reactions and interactions or the effects of various co-morbid conditions. Hence a risk management plan is a mandatory part of the marketing authorisation application for a new drug. Herein the applicant describes potential risks and risks already discovered, as well as the existing gaps in research data. The plan sets out measures to fill the data gaps and to minimise the risks already detected. Data on medicinal safety is replenished according to plan by means of studies planned for each individual problem and information gleaned from adverse reaction reports.

Even though the marketing authorisation holder carries the main responsibility for the safety of the product, the medicines agencies have a significant active role in the continuous production and evaluation of safety data. After the amendments to the EU pharmaceutical legislation have entered into force, the management of pharmacovigilance matters is largely coordinated, irrespective of how the drug has obtained marketing authorisation.

All drugs in use in the EU have been assigned under the responsibility of the regulatory agencies of the various Member States in such a way that each Member State analyses on a monthly basis the safety signals relating to the drugs under its responsibility in the common adverse reactions database. Fimea also processes and evaluates all adverse reaction reports from Finland (Karonen, in this issue).

A separate Pharmacovigilance Risk Assessment Committee (PRAC) was established last year within EMA to deal with matters of pharmacovigilance. The Committee processes all significant drug safety problems and issues an opinion on them.

New safety information may result in changes in the Summary of Product Characteristics, for instance adding new warnings or contraindications, changes in dosage or, in extreme cases, withdrawing the drug from the market. The aim is always to target pharmacotherapy at patients with the most advantageous benefit-to-risk ratio.

Marketing is regulated

Marketing of drugs has its own regulations codified under the Directive on medicinal products. All marketing must be based on the Summary of Product Characteristics approved in connection with the granting of the marketing authorisation. If necessary, Fimea can intervene in the marketing by prohibiting continued marketing in violation of statutes and reinforce such a prohibition with a penalty.

Manufacturing and distribution require permits

The industrial manufacturing of drugs requires a permit from Fimea, as does a pharmaceutical wholesaler, hospital pharmacy or dispensary. Fimea also decides on the setting up, discontinuance or relocation of pharmacies and branch pharmacies. A pharmacist may also apply to Fimea for permission to set up a Pharmacy Service Point. The objective of the permit system is to ensure sufficient coverage of the dispensing network. When a pharmacy licence becomes vacant, applications are invited from licensed pharmacists, and Fimea grants the pharmacy licence to the applicant best meeting the criteria set out in the Medicines Act.

Quality monitored by laboratory

Fimea's laboratory monitors the quality of drugs on the market by random sampling. A network of European quality control laboratories coordinates this operation so as to avoid duplication of work and to enable utilisation of the expertise of the different laboratories.

Inspections ensure the performance of quality systems and the reliability of research results

Fimea regularly inspects all licence holders (pharmaceutical factories, pharmaceutical wholesalers) as well as hospital pharmacies and pharmacies. It is also the task of Fimea to certify and inspect laboratories carrying out preclinical safety trials.

To ensure the reliability of the results of clinical trials, such trials are inspected and compliance with good clinical practice (GCP) is ascertained. Fimea also inspects the pharmacovigilance carried out by marketing authorisation holders.

Particularly for inspections in pharmaceutical factories, inspections hold a strong global dimension: In accordance with the work-sharing within the EU, Fimea's inspectors visit countries outside the EU and inspect the appropriateness of the manufacture of drugs that are

imported to us.

Regulation and the regulation environment are in constant change

Drug safety is a constantly changing issue: new research data is obtained, new drugs may make a former, familiar drug more dangerous than before through interaction, new drugs employed for the same purpose may be less harmful than the former ones. The balance of benefits and risks is related to therapy overall and the evolution taking place there.

Research constantly produces new information on biological phenomena and opens up opportunities for influencing such phenomena with drugs, and we are constantly learning more about the effects of known drugs. Besides the decisions made in pharmaceutical regulation, this knowledge also affects the methods of regulation and regulatory requirements. Hence we must constantly seek a balance between an acceptable level of assurance for knowledge and the availability and cost of novel drugs.

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